THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS: SYNTHESIS AND REACTIONS OF MIXED CARBON, NITROGEN, OXYGEN, AND SULFUR HETEROATOM SYSTEMS

By

HERMAN HOWARD ODENS

A DISSERTATION PRESENTED TO THE GRADUATE SCHOOL
OF THE UNIVERSITY OF FLORIDA IN PARTIAL FULFILLMENT
OF THE REQUIREMENTS FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY

UNIVERSITY OF FLORIDA

2001

Dedicated to my wife Noemi and to my sons Herman Jr., Jake and Jeremy

How much better is it to get wisdom than gold!
And to get understanding rather to be chosen than silver!

Proverbs 16:16, KJV

ACKNOWLEDGMENTS

First of all, I want to thank my Lord Jesus for helping me while completing my Ph.D. degree at UF. With His help, I felt able to go through so many rough times and obstacles. I would like to thank my wife, Noemi, and my sons, Herman Jr., Jake and Jeremy, for all of their love, support, and for making my life meaningful. They will always be the source of my inspiration and a blessing to my days.

Words cannot say how thankful and proud I am of my advisor, Professor Alan R. Katritzky. His guidance, encouragement, knowledge, work values, and his genuine care for my family and me occupy an important place in my life. His mastermind, excellent organization skills and his gentle human sense will always be a true inspiration for me.

My sincere thanks go to my supervisory committee members, Dr. Lisa McElwee-White, Dr. Eric Enholm, Dr. Alexander Angerhofer, and Dr. Ulrich Kurzweg, for their time, suggestions, and help on this project. Thanks go to Dr. Batiste, Dr. Dolbier, Dr. Wright, Dr. Hudlicky and Dr. Williams for their excellence in teaching and tremendous help. I thank Dr. Charles J. Rostek and colleagues at Flexsys America, L. P., for their valuable contributions, ideas, and professional support during our joint investigations.

I want to thank my sub-group leaders, Dr. Henderson, Dr. Voronkov, and Dr. Zhang, for their suggestions and help with my research projects. I also thank Ke Chen, Rex Maimait, Augustine Donkor, Shamal Mehta, Martin Button and specially Douglas Tatham and Alessandro Soares for making work much more enjoyable at the center.

TABLE OF CONTENTS

page

ACKNOWLEDGEMENTS..... iii

ABSTRACT..... vi

CHAPTERS

1. GENERAL INTRODUCTION..... 1

2. MASKED FORMYLATION WITH 2-BENZOTRIAZOLYL-1,3-DIOXOLANE, A NOVEL FORMYL CATION EQUIVALENT

2.1 Introduction..... 5
2.2 Results and Discussion..... 8
2.3 Experimental Section..... 15

3. SYNTHESIS OF *N*-ACYLBENZOTRIAZOLE DERIVATIVES FROM 2-BENZOTRIAZOLYL-1,3-OXATHIOLANE

3.1 Introduction..... 20
3.2 Results and Discussion..... 22
3.3 Experimental Section..... 27

4. SYNTHESES OF NOVEL 2-THIO-5-AMINO SUBSTITUTED BENZOQUINONES

4.1 Introduction..... 30
4.2 Results and Discussion..... 33
4.3 Experimental Section..... 45

5. SYNTHESIS OF A NOVEL CLASS OF BENZOQUINONE DIIMINES

5.1 Introduction..... 52
5.1.1 Published Preparations of *p*-Benzoquinone Diimines..... 53
5.1.2 Published Reactions of *p*-Benzoquinone Diimines..... 59
5.2 Results and Discussion..... 60
5.3 Experimental Section..... 72

6. NOVEL SYNTHESES OF 2,3-DIHYDRO-1,5-BENZOTHIAZEPHIN-4(*5H*)-ONES AND 2H-1,4-BENZOTHIAZIN-3(*4H*)-ONES

6.1 Introduction..... 81
6.2 Results and Discussion..... 84
6.3 Experimental Section..... 94

7. CONCLUSION..... 107

LIST OF REFERENCES..... 109

BIOGRAPHICAL SKETCH..... 119

Abstract of Dissertation Presented to the Graduate School
of the University of Florida in Partial Fulfillment
of the Requirements for the Degree of
Doctor of Philosophy

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS: SYNTHESIS AND REACTIONS OF MIXED CARBON, NITROGEN, OXYGEN, AND SULFUR HETEROATOM SYSTEMS

By

Herman Howard Odens

May, 2001

Chairman: Prof. Alan R. Katritzky
Major Department: Chemistry

A variety of mixed atom heterocycle compounds have been synthetized. Most of the syntheses presented are novel and contribute to a new methodology.

Chapter 2: We investigated the use of new benzotriazole reagent, 2-benzotriazolyl-1,3-dioxolane, as a remarkably stable and versatile electrophilic formylating reagent. We report the use of 2-benzotriazolyl-1,3-dioxolane for the direct electrophilic introduction of a masked aldehyde moiety under very mild conditions.

Chapter 3: The synthesis of *N*-acylbenzotriazole derivatives from 2-benzotriazolyl-1,3-oxathiolane is reported. We propose 2-benzotriazolyl-1,3-oxathiolane as an acyl carbanion equivalent reagent for the direct nucleophilic introduction of a carbonyl moiety.

Chapter 4: 2-Alkylthio-substituted benzoquinones were prepared from benzoquinone and mercaptans in 50-94% yields *via* $NaIO_4$ oxidation of the intermediate hydrobenzoquinones. Subsequent addition of primary and secondary amines, in the presence of air as an oxidizing agent, gave a range of 2-thio-5-amino-substituted benzoquinones. No oxidation at sulfur was detected under the described conditions.

Chapter 5: Various 2-alkylthio-5-amino- and 2,5-bis-amino-1,4-benzoquinone diimines were prepared by treatment of *N*-(1,3-dimethylbutyl)-*N'*-phenyl-1,4-phenylene-diamine with thiols and amines using air as an oxidizing agent. Key 2-alkylthio-1,4-benzoquinone diimines were prepared *via* Ag_2O oxidation of the corresponding 1,4-phenylene diamines.

Chapter 6: A new synthetic approach towards the synthesis of 2,3-dihydro-1,5-benzothiazepin-4(5*H*)-ones and 2*H*-1,4-benzothiazin-3(4*H*)-ones is presented in this paper. Nucleophilic additions of α- and β-mercaptoalkanoate esters and acids to benzoquinone diimines, followed by cyclization with trifluoroacetic acid or 1,3-dicyclohexylcarbodiimide (DCC), provide novel, high yielding syntheses of 2*H*-1,4-benzothiazin-3(4*H*)-ones and 2,3-dihydro-1,5-benzothiazepin-4(5*H*)-ones, respectively.

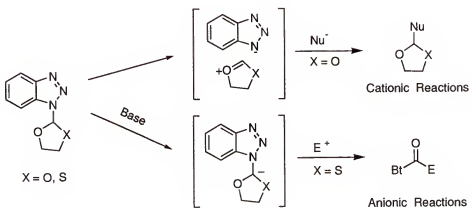
CHAPTER 1
GENERAL INTRODUCTION

Over the past fifteen years, our research group has been involved in the chemistry of benzotriazole as a new synthetic auxiliary capable of offering many synthetic advantages [98CR409]. Several powerful synthetic applications employing benzotriazole derivatives have been developed during this time span and the particular characteristics of such derivatives have been exploited.

Benzotriazole is inexpensive, stable and soluble in many commonly used solvents. It is highly soluble in basic solutions which allows for its easy removal at the end of a synthetic sequence. Due to the conjugated and aromatic nature of the benzotriazole moiety, benzotriazole derivatives are UV active (accounting for easy monitoring of the reaction by thin layer chromatography) and in most cases they have a crystalline physical appearance (allowing for easy purification techniques and stability at normal conditions). Therefore, reaction tracking, work-up and purification are usually really suitable.

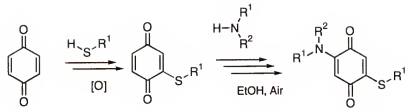
Another interesting feature of benzotriazole chemistry is that the benzotriazole moiety possesses both electron donor and electron acceptor properties. This versatility allows us to employ benzotriazole substituted compounds and perform cationic [89JCS(P1)225, 94JOC7209], anionic [92LA843, 95JA12025, 97JA9321], and radical reactions. Chapters 2 and 3 exemplify experimental work on both cationic and anionic

type of reactions using benzotriazole as a synthetic tool. The scope and limitations of both types of reaction will be discussed in detail.



Scheme 1.1

Another area that will be considered on this work is that of nucleophilic addition to benzoquinoid compounds. Quinoid compounds have played a major role in synthetic chemistry due to their importance in biological systems and industrial applications as well as in electron transfer reactions in general [87MI01]. Chapter 4 will illustrate the addition of mercaptan derivatives to benzoquinone followed by a second nucleophilic addition of an amine to generate 2-thiol-5-amino-substituted benzoquinones. Prior to this work, the synthesis of such compounds having both an N and S heteroatom groups as acyclic substituents has not been achieved by any method in which both heteroatoms are introduced in the benzoquinoid ring by an addition/oxidation protocol.



Scheme 1.2

Benzoquinone diimines [88MI1231] are important compounds due to their many commercial applications such as color photography [77MI339, 70MI663], hair coloring chemistry [73MI103], drug metabolism, and rubber chemistry [86MI159]. The latter area is of great importance in our research group.

Benzoquinone diimines (BQI) bearing both an *N*-alkyl and an *N'*-phenyl group are of particular interest since little work has been done in this area. Addition of nucleophiles to such BQI's, can lead to regiospecific reactions. Since the actual site of attack depends on several factors such as electron density, the stability of the products formed and steric consideration of both the electrophilic site and of the approaching nucleophile, the position for the addition of the incoming nucleophile could be controled. Taking advantage of the fact that our starting BQI's contained an *N*-phenyl group capable of accepting electrons, we prepared several BQI derivatives bearing a substituent introduced regiospecifically at the C-3 position (Chapter 5).

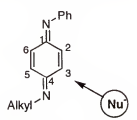


Figure 1.1

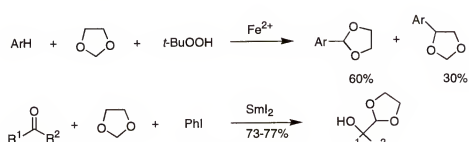
Expansion of this novel methodology, led us into the syntheses of benzothiazepinones and benzothiazinones *via* addition of mercaptan ester derivatives to benzoquinone diimines followed by cyclization. Such derivatives are of great pharmaceutical interest due to the wide spectrum of biological activities that they exhibit. This novel approach will be developed in Chapter 6.

CHAPTER 2
MASKED FORMYLATION WITH 2-BENZOTRIAZOLYL-1,3-DIOXOLANE, A NOVEL FORMYL CATION EQUIVALENT

2.1 Introduction

The direct introduction of a carbonyl moiety, in its protected form, into a multifunctional organic molecule can eliminate an additional protection step and allow the liberation of the masked moiety at a later stage. Such approaches to the introduction of carbonyl functionality are widely used in total synthesis [89MI01]. General methods for the introduction of a masked C-1 aldehyde can be divided into the three classes according to the nature of the reagent $^{\cdot}C$, ^{-}C, or ^{+}C.

The first is exemplified by radical couplings of trioxanes or 1,3-dioxalanes with carbonyl compounds [86JOC536, 87TL5877]. However, these reactions have limited generality and some require conditions (*e.g.*, strong oxidants or SmI_2) which may not be suitable for multifunctional substrates.

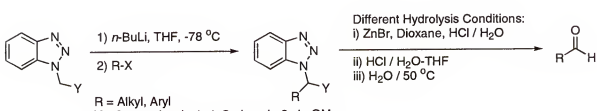


Scheme 2.1

The second class is the most important and widely developed [91MI02]. It includes reactions of electrophiles with many α-heteroatom stabilized formyl anion synthons, typified by deprotonated 1,3-dithiane [66JOC4097], the corresponding sulfones or sulfoxides [71TL3151], α-arylthiotrimethylsilanes [80TL1559] and other α-heteroatom stabilized formyl anion equivalents (Scheme 2.2) [80BCJ3619, 91JOC2143, 98AA35, 76TL4223].

Scheme 2.2

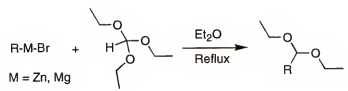
Although some of the previously developed formylating reagents required deprotection by heavy metals or harsh reagents such as *m*-CPBA [80TL1559], or TMSI [82S965], novel α-heteroatom stabilized formyl anion reagents proved to be advantageous due to the very mild deprotection conditions required (Scheme 2.3) [80BCJ3619, 91JOC2143, 98AA35, 93SC3061].



Scheme 2.3

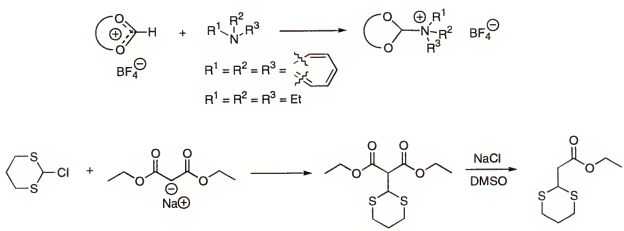
The third strategy is based on reactions of formyl cation equivalents with nucleophiles. Among these, classical reactions of alkyl orthoformates with

organometallics [52JCS4040, 52RTC1021, 47JCS2233] afford the desired dialkyl acetals in 14-81% yields (Scheme 2.4).



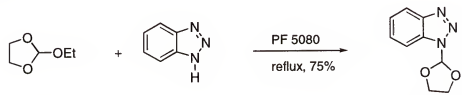
Scheme 2.4

Other formyl cation reagents used with Grignards or organolithiums include (i) α,α-dialkoxy tetraalkylammonium and *N*-alkoxymethylpyridinium salts, which give variable yields [71S312, 61LA641], (ii) 2-chloro-1,3-dithiane and close analogues which form dithiane requiring vigorous conditions to hydrolyze [77TL885, 77TL2077, 86JOM189, 86T3731], and (iii) *N,N*-dialkylformamide acetals used for formylation of enolates (Scheme 2.5)[84KGS1252].



Scheme 2.5

In the present work we investigated the use of new benzotriazole reagent **2.2** as a remarkably stable and versatile electrophilic formylating reagent. We report the use of **2.2** for the direct electrophilic introduction of a masked aldehyde moiety under very mild conditions.

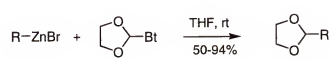


2.1 **2.2**

Scheme 2.6

2.2 Results and Discussion

The key reagent **2.2** was prepared from 2-ethoxydioxolane **2.1** [58CB650] and benzotriazole in 75% yield (Scheme 2.4). Upon treatment with various organozinc reagents **2.2** produced the corresponding products, in 50-94% yields, according to Scheme 2.7.



2.3a-l **2.2** **2.4a-l**

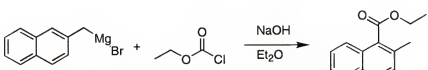
R = Alk, Ar; Bt = Benzotriazol-1-yl.

Scheme 2.7

We used two methods for the *in situ* generation of organozinc reagents **2.3a-l**. In method A the commercial Grignard reagent was treated with an equivalent amount of a 1.0 M solution of $ZnCl_2$ in THF and allowed to stir for 1 h at room temperature. Instead

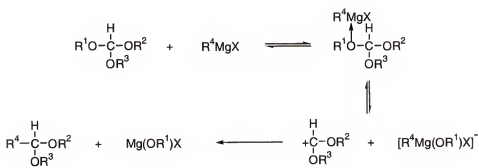
of using a commercial organomagnesium reagent, method B was applied to provide the desired organozinc reagent from the corresponding organohalide. In method B, the organic halide reagent was treated with an equivalent amount of Zn dust and allowed to stir for 1 h (until turning green) in THF at reflux. In both methods, the addition of **2.2** followed by overnight stirring, afforded the desired products **2.4a-l**. All the *sp*, sp^2 and sp^3 nucleophiles tested gave good yields (*e.g.*, entries **2.4a-c,e,f**, Table 2.1). We found that the bulkier secondary alkyl organozinc reagent gave the corresponding product **2.4g** in 57% yield. Unexpectedly product **2.4l** was isolated in 72% yield when organozinc reagent generated from 2-bromomethylnaphthalene was employed.

The NMR spectra of **2.4l** are significantly different from those of **2.4a-k.** The two singlets at 5.20 and 5.13 ppm on 1 H NMR for **2.4l** suggest a terminal double bond; furthermore, the H-2 of the dioxolanyl moiety appeared as a doublet (*J*) 4.1 Hz). Hence **2.4l** was identified as 2-(2-methylene-1,2-dihydro-1-naphthalenyl)-1,3-dioxolane. Such abnormal regioselectivity of addition was previously reported [58ACS1] for reactions of 2-naphthyl-methylmagnesium bromide with a number of electrophiles such as ethyl chlorocarbonate but there are no reports for such behavior of the corresponding organozinc reagents (Scheme 2.8).



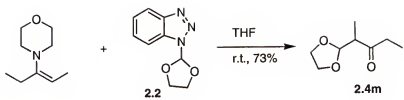
Scheme 2.8

The use of an excess of organozinc reagent is required to achieve reaction completion. For example, when **2.2** was treated with 1.1 equiv of phenylzinc bromide, the yield of the desired product **2.4d** went down to 63%. We also found that reactions of **2.2** with the organozinc reagents gave consistently higher yields than with the corresponding Grignard reagents. When **2.2** was treated with 3 equiv of commercial phenylmagnesium bromide product **2.4d** was isolated in only 55% yield. This may be explained by stronger affinity toward the benzotriazole moiety of organozinc reagents than that of the Grignard reagents [98CR409]. This is consistent with the suggestions of Houghton *et al* [80JCS(P1), 90SC2387] that such chelation activates reagents similar to 2, thus increasing the concentration of dioxolanium ion in the rate-determining step (Scheme 2.9).



Scheme 2.9

Finally, to illustrate the capability of reagent **2.2** to react with electrophiles other than organometallic reagents, we prepared compound **2.4m** in 73% isolated yield from reaction of **2.2** with the enamine 4-(Z)-1-ethyl-1-propenylmorpholine (method C, Scheme 2.10).

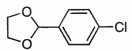
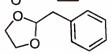
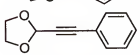
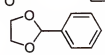
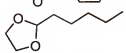
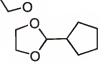
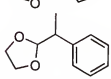
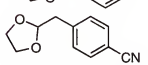
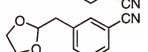
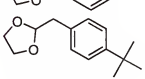
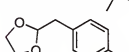
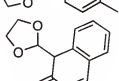
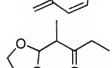


Scheme 2.10

In conclusion, thirteen examples of this new general and efficient method of masked formylation by electrophilic reagent **2.2** have been reported. While the reactivity of **2.2** for the Grignard reagents is comparable to that of other formylating agents, the use of **2.2** is beneficial in reactions with organozinc reagents. The procedure is mild, efficient, and tolerable to multifunctional organic molecules, which makes it suitable for multi-step syntheses.

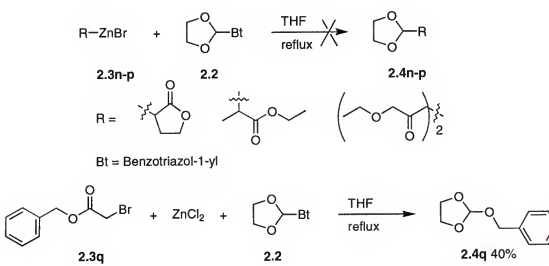
Table 2.1

2-Substituted-1,3-Dioxolane Derivatives

Entry	Product	Yield	Method
2.4a		86%	A
2.4b		70%	A
2.4c		84%	A
2.4d		85%	A
2.4e		83%	A
2.4f		94%	A
2.4g		57%	B
2.4h		54%	B
2.4i		65%	B
2.4j		50%	B
2.4k		64%	B
2.4l		72%	B
2.4m		73%	C

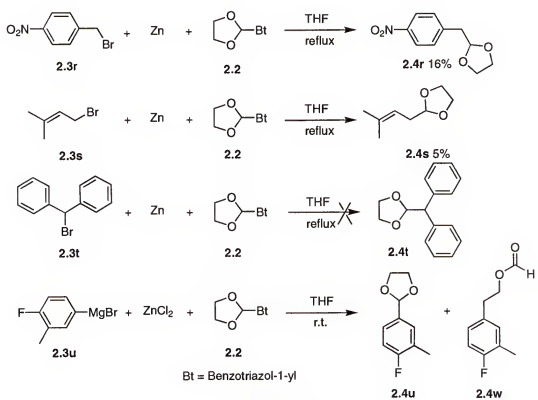
2.2.1 Unsuccessful Attempts

Attempts in introducing Reformatzky type of reactions [47JCS2233] in our Benzotriazole mediated methodology failed. Treatment of 3-bromodihydro-2(3*H*)-furanone (**2.3n**), ethyl 2-bromopropanoate (**2.3o**), diethyl 2-bromomalonate (**2.3p**), and benzyl 2-bromoacetate (**2.3q**) with Zn dust followed by addition of **2.2** did not produce the desired products **2.4n**, **2.4o**, **2.4p**. Instead, the reduced form of the organohalide starting material was recovered most of the time. For the case of the benzyl 2-bromoacetate (**2.3q**), 2-(benzyloxy)-1,3-dioxolane (**2.4q**) was obtained as a clear oil in 40% yield (Scheme 11). The latter case could have been a side product resulting from the formation of a ketene intermediate, allowing a nucleophilic attack by the free alkoxide anion, producing the orthoester **2.4q** in 40% yield.



Scheme 2.11

Attempts in producing 2-(4-nitrobenzyl)-1,3-dioxolane (**2.4r**) from 1-(bromomethyl)-4-nitrobenzene only resulted in 16% yield. 2-(3-methyl-2-butenyl)-1,3-dioxolane (**2.4s**) was obtained in only 5% yield from treatment of 1-bromo-3-methyl-2-butene with **2.2**. A possible explanation for this low yield could have been decomposition of the unsaturated organobromide starting material prior to use. When 1-[bromo(phenyl)methyl]benzene was treated with Zn, followed by addition of compound **2.2**, no desired product (**2.4t**) was collected. Treatment of 4-fluoro-3-methylphenyl magnesium bromide with compound **2.2** produced a hard to separate and to characterize mixture of 2-(4-fluoro-3-methylphenyl)-1,3-dioxolane (**2.4u**) and 4-fluoro-3-methylphenethyl formate (**2.4w**). Scheme 2.12 summarizes these reactions.



Scheme 2.12

2.3 Experimental Section

General Methods. THF was distilled from sodium/benzophenone under nitrogen immediately prior to use. All reactions involving air-sensitive compounds were carried out under an argon atmosphere. Column chromatography was conducted with silica gel 230–400 mesh.

Preparation of 2-Ethoxy-1,3-dioxolane (2.1) [58CB650]: Triethyl orthoformate (96.3 g, 650 mmol) was mixed with ethylene glycol (40.4 g, 650 mmol) and 1 drop of conc. H_2SO_4 was added. The reaction mixture was heated slowly while distilling EtOH, at 78 °C, for 4 h. After EtOH was distilled off from the reaction mixture, the temperature was raised to 142-145 °C and 60.26 g (79.0% yield) of 2-ethoxy-1,3-dioxolane was distilled off as a colorless oil. ^{1}H NMR δ 5.82 (s, 1H), 4.12–4.00 (m, 2H), 3.97–3.92 (m, 2H), 3.59 (q, J = 7.1 Hz, 2H), 1.23 (t, J = 7.1 Hz, 3H); ^{13}C NMR δ 115.0, 63.7, 60.1, 14.8.

1-(1,3-Dioxolan-2-yl)-1*H*-1,2,3-benzotriazole (2.2): 2-Ethoxy-1,3-dioxolane (10.99 g, 93.1 mmol) and benzotriazole (11.08 g, 93.1 mmol) were dissolved in 30 mL of performance fluid (PF 5080) and refluxed at 100 °C, using a reversed Dean-Stark trap. The reaction mixture was stirred and heated for 19 h while EtOH was collected in the trap. The reaction mixture was cooled down and separated from PF 5080 by adding CH_2Cl_2. Unreacted benzotriazole was removed by extracting with of 5% Na_2CO_3 and the reaction mixture was dried over Na_2SO_4 and concentrated using rotary evaporation to yield 1-(1,3-dioxolan-2-yl)-1*H*-1,2,3-benzotriazole (29.8 g, 75%) as a colorless oil. ^{1}H NMR δ 8.10 (d, J = 8.3 Hz, 1H), 7.67 (d, J = 8.2 Hz, 1H), 7.52 (t, J = 7.1 Hz, 1H), 7.40

(t, J = 8.1 Hz, 1H), 7.35 (s, 1H), 4.48–4.22 (m, 4H); ^{13}C NMR δ 158.7, 128.0, 127.0, 124.3, 120.0, 110.5, 105.7, 65.7. HRMS Calcd for $C_9H_9N_3O_2$ (M+1): 192.0695. Found: 192.0773.

General Procedure for Preparation of 2-Alkyl-1,3-dioxolane and 2-Aryl-1,3-dioxalanes. Method A. A 1.0 M solution of zinc chloride (9.30 mL, 9.30 mmol) in THF was added to a flask containing a 1.0 M solution of the corresponding Grignard reagent (9.30 mL, 9.30 mmol) dissolved in 10 mL of THF under nitrogen. The reaction mixture was stirred for 1 h at rt. Formation of a white salt was observed almost immediately. 1-(1,3-dioxolan-2-yl)-1*H*-1,2,3-benzotriazole (0.60 g, 3.1 mmol) was dissolved in 10 mL of THF and added dropwise to the reaction flask. The reaction mixture was stirred overnight at reflux. The reaction mixture was then cooled to room temperature, quenched with 25% NH_4OH, and extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried (Na_2SO_4), filtered (Celite), and the solvent was evaporated. The pure product was obtained by column chromatography using Hexane:EtOAc (9:1).

2-(4-Chlorophenyl)-1,3-dioxolane (**2.4a**): colorless oil; ^{1}H NMR δ 7.41 (d, J = 8.2 Hz, 2H), 7.34 (d, J = 8.5 Hz, 2H), 5.76 (s, 1H), 4.11–3.90 (m, 4H); ^{13}C NMR δ 135.5, 134.9, 128.5, 127.8, 102.9, 65.2; Anal. Calcd for $C_9H_9ClO_2$: C, 58.55; H, 4.92. Found: C, 58.85; H, 4.92.

2-Benzyl-1,3-dioxolane (**2.4b**) [85TL4767]: colorless oil; ^{1}H NMR δ 7.33–7.22 (m, 5H), 5.06 (t, J = 4.9Hz, 1H), 4.03–3.93 (m, 4H), 2.96 (d, J = 4.9 Hz, 2H); ^{13}C NMR δ 137.8, 129.1, 128.3, 126.3, 103.6, 65.2, 40.7.

2-(2-Phenylethynyl)-1,3-dioxolane (2.4c): colorless oil; ^{1}H NMR δ 7.39 (d, J = 5.4 Hz, 2H), 7.37–7.22 (m, 3H), 5.81 (s, 1H), 4.07–3.87 (m, 4H); ^{13}C NMR δ 131.8, 128.9, 128.2, 121.5, 93.4, 85.1, 84.4, 64.5; Anal. Calcd for $C_{11}H_{10}O_2$: C, 75.84; H, 5.80. Found: C, 75.38; H, 5.89.

2-Phenyl-1,3-dioxolane (2.4d) [90JCSP(1)393]: colorless oil; ^{1}H NMR δ 7.40–7.32 (m, 2H), 7.32–7.20 (m, 3H), 5.72 (s, 1H), 4.03–3.90 (m, 4H); ^{13}C NMR δ 137.8, 129.1, 128.3, 126.3, 103.6, 65.2.

2-Pentyl-1,3-dioxolane (2.4e) [90BCJ1258]: colorless oil; ^{1}H NMR δ 5.74 (s, 1H), 4.04–3.85 (m, 4H), 3.44 (t, J = 6.6 Hz, 2H), 1.57–1.45 (m, 2H), 1.30–1.18 (m, 4H), 0.83 (t, J = 6.8 Hz, 3H); ^{13}C NMR δ 115.2, 64.8, 63.8, 29.1, 28.2, 22.3, 13.9.

2-Cyclopentyl-1,3-dioxolane (2.4f) [00JOC1886]: colorless oil; ^{1}H NMR δ 5.85 (s, 1H), 4.34–4.10 (m, 1H), 4.10–3.86 (m, 4H), 1.91–1.63 (m, 6H), 1.63–1.45 (m, 2H); ^{13}C NMR δ 114.8, 77.0, 63.5, 32.6, 23.1.

General Procedure for Preparation of 2-Alkyl-1,3-dioxolane and 2-Aryl-1,3-dioxalanes. Method B. Zn dust (1.6 g, 24.5 mmol) was freshly activated by washing with 2% HCl, MeOH, Et_2O, dried in a vacuum oven at 100 °C for 30 min, then used immediately after cooling under argon. Ten mL of dried THF was added to the zinc followed by addition of the corresponding alkyl bromide (3.2 mmol) in 5 mL of THF. The reaction mixture was allowed to reflux for 1 h. 1-(1,3-dioxolan-2-yl)-1H-1,2,3-benzotriazole (0.61 g, 3.2 mmol) was dissolved in 10 mL of THF and added dropwise to the reaction flask. The reaction mixture was stirred overnight at reflux, cooled to room

temperature, quenched with 25% NH_4OH, then extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried (Na_2SO_4), filtered (Celite), and the solvent was evaporated. The pure product was obtained by column chromatography using hexane:EtOAc (9:1).

2-(1-Phenylethyl)-1,3-dioxolane (2.4g) [85TL4767]: colorless oil; ^{1}H NMR δ 7.34–7.20 (m, 5H), 4.98 (d, J = 4.6 Hz, 1H), 3.99–3.79 (m, 4H), 2.99-2.97 (m, 1H), 1.34 (d, J = 7.1 Hz, 3H); ^{13}C NMR δ 142.1, 128.2, 128.1, 126.6, 107.2, 65.1, 43.8, 15.4.

4-(1,3-Dioxolan-2-ylmethyl)benzonitrile (2.4h): white crystals; mp 68-70 °C; ^{1}H NMR δ 7.58 (d, J = 8.2 Hz, 2H), 7.39 (d, J = 8.2 Hz, 2H), 5.08 (t, J = 4.6 Hz, 1H), 3.93–3.81 (m, 4H), 3.02 (d, J = 4.4 Hz, 2H); ^{13}C NMR δ 141.5, 131.8, 130.5, 118.8, 110.3, 103.4, 64.9, 40.5; Anal. Calcd for $C_{11}H_{11}NO_2$: C, 69.82; H, 5.87. Found: C, 69.57; H, 6.05.

3-(1,3-Dioxolan-2-ylmethyl)benzonitrile (2.4i): colorless oil; ^{1}H NMR δ 7.58 (s, 1H), 7.52 (d, J = 7.2 Hz, 2H), 7.40 (t, J = 7.4 Hz, 1H), 5.07 (t, J = 4.3 Hz, 1H), 3.95–3.82 (m, 4H), 3.00 (d, J = 4.3 Hz, 2H); ^{13}C NMR δ 137.4, 134.4, 133.3, 130.2, 128.9, 118.8, 112.1, 103.5, 65.0, 40.0; Anal. Calcd for $C_{11}H_{11}NO_2$: C, 69.82; H, 5.87; N, 7.40. Found: C, 69.75; H, 5.98; N, 7.45.

2-[4-(*tert*-Butyl)benzyl]-1,3-dioxolane (2.4j): colorless oil; ^{1}H NMR δ 7.33 (d, J = 7.9 Hz, 2H), 7.21(d, J = 7.9 Hz, 2H), 5.05 (t, J = 4.9 Hz, 1H), 3.96–3.83 (m, 4H), 2.94 (d, J = 4.9 Hz, 2H), 1.30 (s, 9H); ^{13}C NMR δ 149.2, 133.0, 129.1, 125.2, 104.8, 64.9, 40.2, 34.3, 31.3; Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.32; H, 9.17. Found: C, 75.97; H, 9.52.

2-(4-Methylbenzyl)-1,3-dioxolane (2.4k): colorless oil; ^{1}H NMR δ 7.17-7.09 (m, 4H), 5.02 (t, J = 4.7 Hz, 1H), 3.95–3.80 (m, 4 H), 2.92 (d, J = 4.7 Hz, 2H), 2.31 (s, 3H); ^{13}C NMR δ 136.0, 132.9, 129.4, 128.9, 104.7, 64.8, 40.2, 21.0; Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.12; H, 7.93. Found: C, 74.40; H, 8.39.

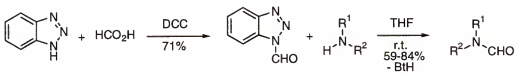
2-(2-Methylene-1,2-dihydro-1-naphthalenyl)-1,3-dioxolane (2.4l): white crystals; mp 148-150 °C; ^{1}H NMR δ 7.25–7.04 (m, 4H), 6.37 (d, J = 21.3 Hz, 1H), 6.33 (d, J = 21.3 Hz, 1H), 5.20 (s, 1H), 5.13 (s, 1H), 4.91 (d, J = 4.1 Hz, 1H), 3.80–3.70 (m, 4H), 3.69–3.59 (m, 1H); ^{13}C NMR δ 141.4, 133.5, 133.2, 129.6, 128.4, 127.6, 127.1, 126.5, 117.0, 108.0, 65.2, 64.9, 49.7; HRMS Calcd for $C_{14}H_{14}O_2$ (M+1): 215.0994. Found: 215.1072.

Preparation of 2-(1,3-Dioxolan-2-yl)-pentan-3-one (2.4m) [90JA8215]**. Method C**: 4-[(z)-1-Ethyl-1-propyl]morpholine (0.49 g, 3.2 mmol) was dissolved in 10 mL of anhydrous THF and 1-(1,3-dioxolan-2-yl)-1*H*-1,2,3-benzotriazole (0.61 g, 3.2 mmol) was added, followed by 1.1 equivalent of $ZnBr_2$ solution in ether. After 5 h the solvent was removed and the product was distilled on Kugelrohr at 75 °C/.5 mm Hg to yield 73%. ^{1}H NMR δ 4.91 (d, J = 5.8 Hz, 1H), 3.95–3.81 (m, 4H), 2.80–2.70 (m, 1H), 2.49 (q, J = 6.1 Hz, 2H), 1.09 (d, J = 6.9 Hz, 3H), 0.98 (t, J = 6.1 Hz, 3H); ^{13}C NMR δ 211.8, 104.7, 65.0, 64.8, 35.9, 32.6, 11.7, 7.2.

CHAPTER 3
SYNTHESIS OF *N*-ACYLBENZOTRIAZOLE DERIVATIVES FROM 2-BENZOTRIAZOLYL-1,3-OXATHIOLANE

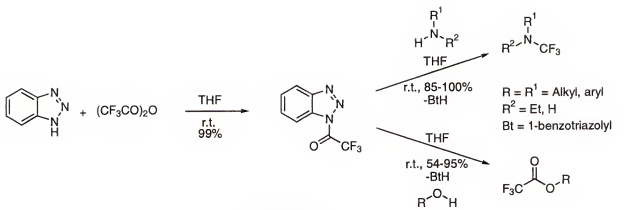
3.1 Introduction

The chemistry of the carbonyl group in organic synthesis plays an important role in the preparation of useful substrates. The versatile benzotriazole synthon continues to provide new synthetic routes for the preparation of compounds bearing a carbonyl group attached to a benzotriazolyl group which can then be transformed into a useful substrate by elimination of the benzotriazolyl moiety [94S445, 91T2683]. Our group has recently reported the use of formylbenzotriazole as a good formylating agent (Scheme 3.1)[95S503].



Scheme 3.1

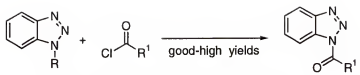
1-(Arylacetyl)benzotriazoles were employed as precursors of arylketenes [96HAC365] for preparation of symmetrical ketones and arylbenzyl sulfoxides [96SL701], and (trifluroacetyl)benzotriazole (Scheme 3.2) has been used as a novel and facile trifluoroacetylating reagent for amines and alcohols [97JOC726].



Scheme 3.2

Treatment of diketene with benzotriazole has been shown to produce 1-(benzotriazole-1-yl)butane-1,3-dione [90JCS(P1)1717] and most recently, a general synthesis of unsymmetrical tetrasubstituted oxamides via 1,1'-(1,2-dioxoethane-1,2-diyl)bis –1*H*-benzotriazole has been reported [98S153].

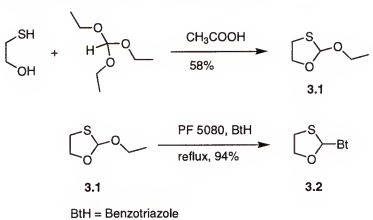
N-Acylbenzotriazole derivatives can be synthesized from acids, by treating acyl chlorides prepared *in situ* with (i) benzotriazole in the presence of a base such as triethylamine [96HAC365] or pyridine [70TL1457] or by fusion of benzotriazole and acyl chloride without any solvent [92T7817]; by reaction with (ii) 1-(trimethylsilyl)benzotriazole [80JOM141]; with (iii) 1-(tributylstannyl)benzotriazole [77JOM185] (Scheme 3.3); and with (iv) 1-(hydroxymethyl)benzotriazole which loses formaldehyde [54JA285]. *N*-Acylbenzotriazoles can also be prepared in high yields directly from carboxylic acids, by their reaction with 1-(methanesulfonyl)benzotriazole [92T7817].



R = H, -SiMe$_3$, -SO$_2$CH$_3$ or -SO$_2$Ph, -SnBu$_3$
R^1 = Alkyl, aryl, heteroyl

Scheme 3.3

We now present a novel synthetic route to produce *N*-acylbenzotriazole derivatives from 2-benzotriazolyl-1,3-oxathiolane **3.2**. We would like to report **3.2** as an acyl carbanion equivalent reagent [78TL2345, 77S357, 76T1943, 74CIL687, 65AGE1075] for the direct nucleophilic introduction of a carbonyl moiety. The reaction of **3.2** with lithium diisopropylamide reacts predictably with organic electrophiles to yield products in which the protected carbonyl group is readily unmasked.



Scheme 3.4

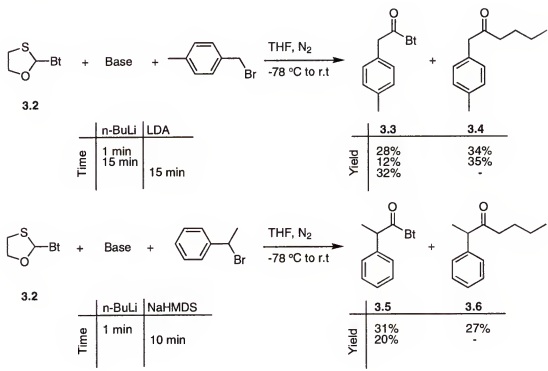
3.2 Results and Discussion

Treatment of 2-mercaptoethanol with triethyl orthoformate and a catalytic amount of glacial acetic acid gave 2-ethoxy-1,3-oxathiolane (**3.1**) [77MI276] in 58% yield as a

colorless oil. The addition of glacial acetic acid proved to be necessary for the formation of **3.1**. The use of one drop of concentrated sulfuric acid was unsuccessful. Compound **3.1** was then mixed with an equivalent amount of benzotriazole in performance fluid (PF 5080) and the reaction mixture was allowed to reflux overnight [95H131]. 2-Benzotriazolyl-1,3-oxathiolane **3.2** was obtained in 94% yield (Scheme 3.4).

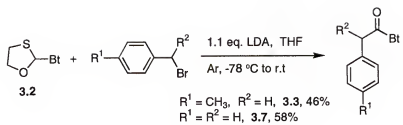
We shifted our attention to the addition of electrophiles to compound **3.2**. When compound **3.2** was treated with n-BuLi and allowed to stir at –78 °C in THF for 1 minute, followed by addition of 1-bromomethyl)-4-methylbenzene, the compounds 1-(1*H*-1,2,3-benzotriazol-1-yl)-2-(4-methylphenyl)-1-ethanone (**3.3**), and 1-(4-methylphenyl)-2-hexanone (**3.4**) were obtained in 28% and 34% respectively. Initially, it appeared that the competing product **3.4** was favored because deprotonation of compound **3.2** did not go to completion in 1 minute, thus allowing unreacted *n*-BuLi to displace benzotriazole from the non-hydrolyzed Bt-adduct intermediate. Thus, the same reaction was repeated, but this time, *n*-BuLi was added dropwise and allowed to stir for 15 minutes at –78 °C in THF. The results were less encouraging, since **3.3** and **3.4** were recovered in 12% and 35% respectively. When LDA was employed instead of *n*-BuLi and allowed to stir for 15 minutes at –78 °C in THF, only compound **3.3** was recovered as expected, but just a 32% yield was obtained. A similar trend was observed in the formation of 1-(1*H*-1,2,3-benzotriazol-1-yl)-2-phenyl-1-propanone (**3.5**), and 2-phenyl-3-heptanone (**3.6**). When compound **3.2** was treated with *n*-BuLi and allowed to stir at –78 °C in THF for 1 minute, compounds **3.5** and **3.6** were formed in 31% and 27% yield respectively. Treating compound **3.2** with NaHMDS instead of *n*-BuLi and allowing the reaction to stir for 10 min at –78 °C in THF gave compound **3.5** in 20% yield. We then concluded that LDA

gave the best results and that using fresh LDA would improve the yields. A summary of all of these results is depicted in Scheme 3.5.



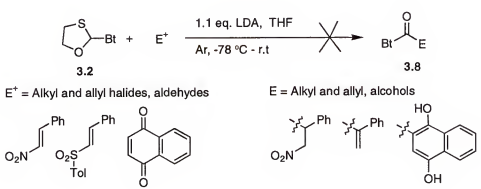
Scheme 3.5

When compound **3.2** was dissolved in THF and mixed with an electrophile followed by the addition of 1.1 equivalents of fresh LDA and stirring overnight from –78 °C to room temperature, *N*-acylbenzotriazole derivatives were synthesized directly after mildly acidic workups. The above procedure resulted in the best reaction conditions. When α-bromo-*p*-xylene and benzyl bromide were used, 1-(1*H*-1,2,3-benzotriazol-1-yl)-2-(4-methylphenyl)-1-ethanone (**3.3**), and 1-(1*H*-1,2,3-benzotriazol-1-yl)-2-phenyl-1-ethanone (**3.7**) [96HC365]were obtained in 46% and 58% yields respectively (Scheme 3.6).



Scheme 3.6

Compound **3.2** was then treated with different electrophiles such as alkyl bromides, aldehydes, 1-[(*E*)-2-nitroethenyl]benzene, 4-methylphenyl (*E*)-2-phenylethenyl sulfone, and naphthoquinones to obtain some functionalized benzotriazole derivatives such as **3.8** (Scheme 3.7). However, none of these reactions proceeded to give the expected products. Instead, decomposition of **3.2** was observed as shown by the recovery of large amounts of BtH present after workup, and in some instances, elimination product from the alkylbromides derivatives was also observed. A summary of all unsuccessful reactions is depicted in Scheme 3.4.



Scheme 3.7

In summary we have introduced a novel synthetic route to produce *N*-acylbenzotriazole derivatives not available from the corresponding acid or acyl chloride by means of an acyl carbanion equivalent. However, this method is limited in that it gives us the opportunity to produce *N*-acylbenzotriazoles from benzylic halides as electrophiles.

3.4 Experimental Section

Melting points were determined with a MEL-TEMP capillary melting point apparatus equipped with a Fluke 51 digital thermometer. NMR spectra were taken in $CDCl_3$ with tetramethylsilane as the internal standard for ^1H (300 MHz) or solvent as the internal standard for ^{13}C (75 MHz). THF was distilled from sodium/benzophenone under nitrogen immediately prior to use. All reactions were carried out under an argon atmosphere. Column chromatography was conducted with silica gel 230–400 mesh.

Preparation of 2-Ethoxy-1,3-oxathiolane (3.1) [77MI276]. A mixture of 2-mercaptoethanol (39.0 ml, 500 mmol), triethyl orthoformate (74.1 g, 500 mmol), and glacial acetic acid (1.33 g, 22.2 mmol) was brought to reflux for 1 min. Immediately, the EtOH formed in the reaction was continuously removed by distillation at 100 ° C, for 4 h. After the EtOH was driven off from the reaction mixture, the organic residue was poured into a large quantity of an aqueous solution of 5% NaOH. The aqueous layer was then washed with 2 x 50 mL of CH_2Cl_2, the organic layers were combined, dried ($MgSO_4$), filtered (Celite), and the CH_2Cl_2 was distilled, at 40 °C. The distillation of the desired product was performed using a water aspirator and it distilled at 120-132 °C / 18mm Hg. 2-Ethoxy-1,3-oxathiolane was collected as a clear oil (37.8 g, 58% yield). ^1H NMR δ 6.29 (s, 1H), 4.28-4.22 (m, 1H), 4.16-4.08 (m, 1H), 3.75-3.70 (s, J = 7.0 Hz, 1H), 3.69-3.52 (s, J = 7.0 Hz, 1H), 3.18-3.11 (m, 1H), 3.04-2.95 (m, 1H), 1.24 (t, J = 7.0 Hz, 1H); ^{13}C NMR δ 109.2, 68.9, 63.2, 32.3, 14.9.

2-Benzotriazolyl-1,3-oxathiolane (3.2): 2-Ethoxy-1,3-oxathiolane **3.1** (37.6 g, 280 mmol) and benzotriazole (27.9 g, 280 mmol) were disolved in 20 mL of performance fluid (PF 5080) and refluxed at 100 °C, using a reversed Dean Stark apparatus. The reaction mixture was stirred and heated for 19 h while EtOH was collected in the trap. The reaction mixture was then cooled and separated from PF 5080 by adding 100 mL of CH_2Cl_2 and extracting with 3 x 50 mL of 5% Na_2CO_3. 2-Benzotriazolyl-1,3-oxathiolane (44.7 g, 92%) was obtained as a colorless oil. ^{1}H NMR δ 8.10-8.08 (d, J = 8.1 Hz, 1H), 7.76-7.73 (m, 2H), 7.52 (t, J = 7.1 Hz, 1H), 7.41 (t, J = 7.4 Hz, 1H), 4.58-4.53 (m, 1H), 4.35-4.28 (m, 1H), 3.61-3.53 (m, 1H), 3.40-3.33 (m, 1H); ^{13}C NMR δ 146.7, 131.5, 127.7, 127.1, 124.4, 120.2, 111.0, 93.3, 72.0, 33.6. HRMS Calcd for $C_9H_9N_3OS$ (M+1): 208.0545. Found: 208.0574.

General Procedure for Preparation of *N*-Acylbenzotriazole. 2-Benzotriazolyl-1,3-oxathiolane **3.2** (0.62 g, 3.0 mmol) and benzylic halide (0.61 g , 3.3 mmol) were mixed inside an airless flask and dissolved in 15 mL of freshly distilled THF at -78 °C. LDA was added dropwise and the reaction mixture was allowed to stir overnight from -78 °C to r.t. The reaction was quenched with 20 mL of NH_4Cl, then extracted with 3 x 30 mL of CH_2Cl_2. The organic layer was dried (Na_2SO_4), filtered (Celite), and the solvent was evaporated. Pure product was obtained after column chromatography using Hex:EtOAc (9:1) and (1:1).

1-(1H-1,2,3-Benzotriazol-1-yl)-2-(4-methylphenyl)-1-ethanone (3.3): yellow crystals; mp 76-78 °C. ^{1}H NMR δ 8.03 (d, J = 8.2 Hz, 1H), 7.37-7.29 (m, 3H), 7.18-7.10 (m, 4H), 5.78 (s, 2H), 2.29 (s, 3H); ^{13}C NMR δ 160.5, 146.2, 138.1, 132.6, 131.6, 129.5, 127.5,

127.2, 123.7, 119.8, 109.7, 51.9, 21.0. Anal. Calcd for $C_{15}H_{13}N_3O$: N, 16.72. Found: N, 16.53.

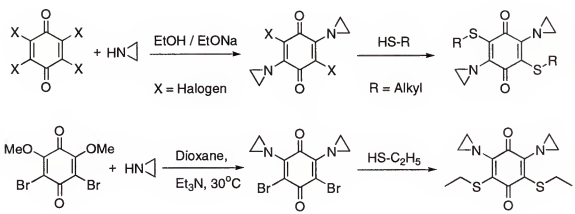
1-(1H-1,2,3-Benzotriazol-1-yl)-2-phenyl-1-ethanone (3.7) [96HC365]: yellow crystals; mp 67-70 °C. ^{1}H NMR δ 8.05 (d, J = 7.1 Hz, 1H), 7.41-7.24 (m, 9H), 5.82 (s, 2H); ^{13}C NMR δ 160.5, 146.1, 134.6, 132.6, 129.1, 128.0, 127.4, 127.3, 123.8, 119.8, 109.6, 51.9.

CHAPTER 4
SYNTHESES OF NOVEL 2-THIO-5-AMINO SUBSTITUTED BENZOQUINONES

4.1 Introduction

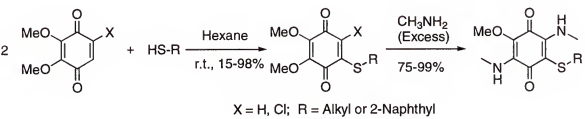
In the course of ongoing research in the area of rubber additives we were interested in the preparation of 5-amino-2-alkylthio-substituted 1,4-benzoquinones. Two obvious strategies to prepare these compounds are based on the different order of introduction of the desired substituents onto the quinone core.

In the first and previously more generally applied approach, the nitrogen substituent is introduced first usually *via* displacement of a halogen or an alkoxy group from the appropriate quinone. The thiol moiety is then introduced by displacement of another halide or alkoxy moiety on the same quinone [55AG217, 57AG252, 57HCA502] (Scheme 4.1) or by an addition/oxidation route [73TL4696].



Scheme 4.1

In the second somewhat less widely accepted strategy, the nitrogen substituent is introduced into an alkylthio-substituted benzoquinone *via* amine displacement of a leaving group, usually an alkoxide. Excess of the amine can introduce a second amino substituent (Scheme 4.2) [77MI171].

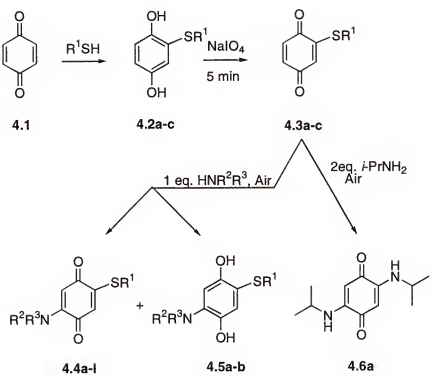


Scheme 4.2

Both these strategies require the presence of at least two good leaving groups in the starting quinone, thus limiting their scope and accessibility. Surprisingly, no reference was found for the preparation of 5-amino-2-alkylthio-substituted 1,4-benzoquinones by sequential introduction of both substituents *via* an addition/oxidation protocol. The order of addition is important, because introduction of an amine moiety by the oxidation/addition route into an unsubstituted benzoquinone frequently [48JA861, 56JA1233, 10CB525], although not invariably [94S917], results in bis adducts. However, 2-alkylthio-substituted benzoquinones, which should be good precursors for 5-amino-substituted 2-alkylthio-1,4-benzoquinones, are readily available from 1,4-benzoquinones by two general methods. The more common utilizes the reaction of the corresponding mercaptan with a benzoquinone in the presence of diverse oxidants. The following oxidants have been used: excess of the starting benzoquinone [89JCSP(1)179], oxygen [94JA1691], $CuSO_4$ [88CGC608], $FeCl_3$ [49JA1124], $NaIO_4$ [83JOC4764] and silica gel

supported $NaIO_4$ [81JCSP(1)2970], Fremy's salt, $Pb(OAc)_4$ and CAN [88MI01]. The second method deals with reactions of the corresponding chloroquinones with thiols [88MI01, 86MI02, 89MI02, 98MI587].

We now report that a wide variety of 2-alkylthio-5-amino-1,4-benzoquinones **4.4a-l** can be obtained in satisfactory yields by using the addition/oxidation protocol shown in Scheme 4.3.



Scheme 4.3

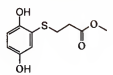
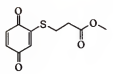
4.2 Results and Discussion

Reactions of the appropriate mercaptans with benzoquinone (**4.1**) in ethanol afforded the corresponding 2-alkylthiohydroquinones **4.2a-c** (Table I). While **4.2a-c** are all solid, both **4.2a** and **4.2b** melt close to room temperature, hindering their recrystallization. Compounds **4.2a-c** were identified by the signals of *C-1* and *C-4* in the 148.6-151.4 ppm region of ^{13}C NMR spectra which are characteristic for asymmetric hydroquinones [74MI001]. Furthermore, the expected three proton signals were observed in the aromatic region of the ^{1}H NMR spectra for **4.2a-c**.

Reactions of **4.2a-c** with stoichiometric amounts of $NaIO_4$ in the presence of a catalytic amount of benzyltrimethylammonium bromide yielded the desired compounds **4.3a-c** in 16-76% yields (Table 4.1). Reaction of **4.2b** with a catalytic amount of $NaIO_4$ and a stoichiometric amount of H_2O_2 in the presence of a catalytic amount of benzyltrimethylammonium bromide gave the desired compound **4.3b** in 40% yield after 10 minutes of stirring. In contrast, no reaction took place with H_2O_2 in the absence of $NaIO_4$. Other oxidants such as benzoquinone [91JOC5808] or $FeCl_3$ [49JA1124] were less effective and afforded 10-54% of the desired products. Furthermore, use of an excess of benzoquinone as an oxidant requires tedious isolation and purification of the desired compounds. Pure 2-(cyclohexylsulfanyl)-1,4-benzoquinone (**4.3b**) crystallized from the reaction mixture; 2-alkylthio-1,4-benzoquinones **4.3a,c** were isolated by column chromatography. 2-Alkylthio-1,4-benzoquinones **4.3a-c** have characteristic proton signals at 6.38-6.43 ppm and two carbonyl signals at 183.7-187.2 ppm in the ^{1}H NMR and ^{13}C NMR spectra respectively.

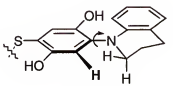
Table 4.1

2-Alkylthio-substituted Hydroquinones and Benzoquinones

#	Compound	#	Compound
4.2a		**4.3a**	
4.2b		**4.3b**	
4.2c		**4.3c**	

The desired 2-thio-5-amino benzoquinones **4.4a-l** (Table 4.2) were obtained in 70-97% yields by treatment of **4.3a-c** with the appropriate amines in the presence of air as an oxidant. Compounds **4.4a-l** are colored and crystalline with melting points of 113.0-208.0 °C. They were purified by crystallization from appropriate solvents. When **4.3a** was treated with 2,3-dihydroindole no desired quinone was formed. Instead, methyl 3-(4-[1,2,3,4-tetrahydro-1-quinolinyl]-2,5-dihydroxyphenylsulfanyl) propanoate **4.5a** was isolated as a black oil by column chromatography in 72% yield. The unexpected stability of **4.5a** toward oxidation by air can perhaps be explained by the poor overlap of the lone pair of the nitrogen with the hydroquinonoid ring π-system resulting from unfavorable

steric interactions of the methylene group of the tetrahydroquinoline substituent and *H-3* of the dihydroquinonoid ring (Figure 1). This would lower the electron donor abilities of the substituents and consequently the HOMO energy of the system and significantly reduce the reactivity of **4.5a** toward oxidation. When **4.3a** was treated with *N*-phenyl-1,4-phenylenediamine, the corresponding hydroquinone **4.5b** was obtained. This result is hard to interpret especially due to structural similarities between **4.5b** and **4.4a**.



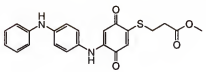
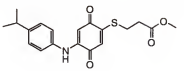
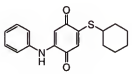
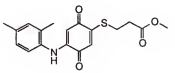
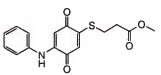
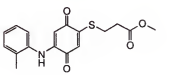
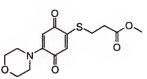
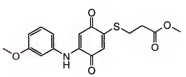
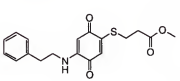
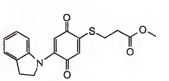
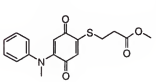
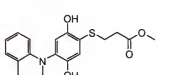
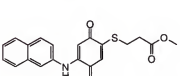
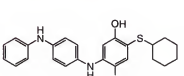
4.5a

Figure 1

The 2-thio-5-aminobenzoquinones **4.4a-l** each show two distinctive singlets for *H-2* and *H-6* in the 5.53-6.52 region of the ^{1}H NMR spectra. The quinonoid proton shifted upfield is identified as *H-6*. The chemical shift of the *H-2* signal is consistent with that of the parent 2-alkylthio-1,4-benzoquinones **4.3a-c**.

Table 4.2

2-Alkylthio-5-amino-substituted 1,4-Benzoquinones and Hydroquinones

#	Compound	#	Compound
4.4a		**4.4h**	
4.4b		**4.4i**	
4.4c		**4.4j**	
4.4d		**4.4k**	
4.4e		**4.4l**	
4.4f		**4.5a**	
4.4g		**4.5b**	

The UV spectra of all the hydroquinones and quinones were taken in acetonitrile on Spectral Instruments 440 Fiber Optic Spectrophotometer. As expected the introduction

of the heteroatom substituents results in a bathochromic shift of all absorptions, especially the second $\pi \rightarrow \pi^*$ transition [74MI001, 88CGC608]. This can be explained by redistribution of the electron density in the molecule caused by the presence of strong electron donating substituents. For 2-thio-substituted quinones **4.3a-c** the wavelengths and intensities were in line with those reported in the literature (Table 4.3) [49JA1124]. The wave-lengths and intensities of the principal maxima were as follows: 201-210 nm ($14800 < \varepsilon < 15400$), 243-252 nm ($6680 < \varepsilon < 8280$), 307-378 nm ($1440 < \varepsilon < 2530$), 412-434 nm ($1190 < \varepsilon < 2240$). Subsequent introduction of a nitrogen substituent resulted in a significant bathochromic shift of the second transition to the 256-298nm ($10200 < \varepsilon < 32000$) range, as well as in an increase in the absorption coefficients. We also found that quinones **4.4d,f,l** where the substituents are not capable of hydrogen bonding have UV spectra very similar to the rest of nitrogen substituted quinones (Table 4.4) [74MI001].

Table 4.3

UV/Visible Data for 2-Alkylthio-substituted 1,4-Benzoquinones

Compound	Concentration	Wavelengths	Absorbance	Absortivity Coefficients
4.2a	1.00E-05	209	0.171	1.71E+04
	1.00E-05	303	0.056	5.60E+03
	1.00E-05	372	0.007	7.00E+02
	1.00E-05	452	0.007	7.00E+02
4.2b	1.00E-05	206	0.31	3.10E+04
	1.00E-05	227	0.084	8.40E+03
	1.00E-05	253	0.022	2.20E+03
	1.00E-05	308	0.079	7.90E+03
	1.00E-05	360	0.008	8.00E+02
4.2c	1.00E-04	226	0.906	9.06E+03
	1.00E-04	299	0.337	3.37E+03
	1.00E-04	378	0.084	8.40E+02
4.3a	1.00E-04	210	1.544	1.54E+04
	1.00E-04	252	0.828	8.28E+03
	1.00E-04	311	0.144	1.44E+03
	1.00E-04	424	0.294	2.94E+03
4.3b	1.00E-04	243	2.19	2.19E+04
	1.00E-04	378	0.255	2.55E+03
	1.00E-04	434	0.154	1.54E+03
4.3c	1.00E-04	201	1.482	1.48E+04
	1.00E-04	208	1.421	1.42E+04
	1.00E-04	225	1.136	1.14E+04
	1.00E-04	251	0.668	6.68E+03
	1.00E-04	307	0.231	2.31E+03
	1.00E-04	412	0.119	1.19E+03

Table 4.4

UV/Visible Data for 2-Alkylthio-5-Amino-Substituted 1,4-Benzoquinones

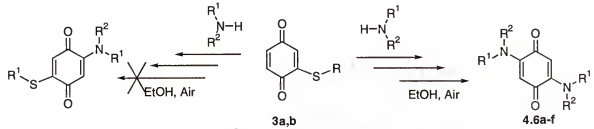
Compound	Concentration	Wavelengths	Absorbance	Absortivity Coefficients
4.4a	1.00E-05	203	0.527	5.27E+04
	1.00E-05	296	0.302	3.02E+04
	1.00E-05	347	0.176	1.76E+04
	1.00E-05	421	0.075	7.50E+03
	1.00E-05	573	0.048	4.80E+03
4.4b	1.00E-04	263	1.065	1.07E+04
	1.00E-04	292	0.605	6.05E+03
	1.00E-04	373	1.028	1.03E+04
	1.00E-04	501	0.174	1.74E+03
4.4c	1.00E-04	226	1.838	1.84E+04
	1.00E-04	362	1.084	1.08E+04
	1.00E-04	513	0.082	8.20E+02
4.4d	1.00E-04	362	1.486	1.49E+04
	1.00E-04	516	0.119	1.19E+03
4.4e	1.00E-05	216	0.376	3.76E+04
	1.00E-05	350	0.283	2.83E+04
	1.00E-04	501	0.09	9.00E+02
4.4f	1.00E-05	219	0.193	1.93E+04
	1.00E-05	252	0.147	1.47E+04
	1.00E-05	363	0.183	1.83E+04
	1.00E-04	516	0.193	1.93E+03
4.4g	1.00E-05	217	0.632	6.32E+04
	1.00E-05	262	0.32	3.20E+04
	1.00E-05	322	0.09	9.00E+03
	1.00E-05	362	0.159	1.59E+04
	1.00E-05	529	0.029	2.90E+03
4.4h	1.00E-05	213	0.188	1.88E+04
	1.00E-05	264	0.145	1.45E+04
	1.00E-05	371	0.162	1.62E+04
	1.00E-05	536	0.015	1.50E+03

Table 4.4--continued

Compound	Concentration	Wavelengths	Absorbance	Absortivity Coefficients
4.4i	1.00E-05	213	0.283	2.83E+04
	1.00E-05	256	0.113	1.13E+04
	1.00E-05	358	0.195	1.95E+04
	1.00E-05	524	0.012	1.20E+03
4.4j	1.00E-05	213	0.31	3.10E+04
	1.00E-05	256	0.102	1.02E+04
	1.00E-05	358	0.199	1.99E+04
	1.00E-05	523	0.01	1.00E+03
4.4k	1.00E-05	219	0.44	4.40E+04
	1.00E-05	262	0.185	1.85E+04
	1.00E-05	366	0.2	2.00E+04
	1.00E-04	529	0.207	2.07E+03
4.4l	1.00E-05	214	0.215	2.15E+04
	1.00E-04	279	1.59	1.59E+04
	1.00E-04	390	0.989	9.89E+03
	1.00E-04	582	0.342	3.42E+03
4.5a	1.00E-05	209	0.296	2.96E+04
	1.00E-05	254	0.1	1.00E+04
	1.00E-05	313	0.067	6.70E+03
	1.00E-05	382	0.037	3.70E+03
	1.00E-05	562	0.003	3.00E+02
4.5b	1.00E-05	202	0.498	4.98E+04
	1.00E-05	294	0.31	3.10E+04
	1.00E-05	349	0.137	1.37E+04
	1.00E-05	434	0.074	7.40E+03
	1.00E-05	552	0.042	4.20E+03

4.2.1 Unsuccessful Attempts

Alkyl and aryl primary amines both react with **4.3a-c** to afford the corresponding products **4.4a-l** in comparable yields. Little difference was found between the reactivity of primary and secondary amines. The reaction is stoichiometric in respect to most of amines. However, similarly to the reactivity of other quinones [48JA861, 56JA1233], reaction of **4.3a-c** with strongly basic alkylamines takes place resulting in the displacement of a 2-thio-substituent by the amine, most likely via Michael addition/elimination mechanism (Scheme 4.4). In all cases, the 2,5-bis-alkylamino-1,4-benzoquinone **4.6a-f** were recovered as the major product along with some starting material. These results suggest that the more nucleophilic alkylamines also displace the thiol group at the 2-position after the first 1,4-addition at the 5-position takes place.



R = 4.3a $R^1 = R^2$ = 4.6a, 45%

R = cyclohexyl 4.3b R^1 = H, R^2 = *n*-butyl **4.6b**, 48%

R = 4.3a R^1 = H, R^2 = *t*-octyl **4.6c**, 50%

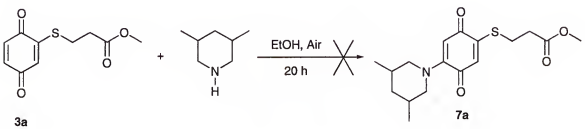
R = 4.3a R^1 = ethyl, R^2 = propyl **4.6d**, 54%

R = 4.3a $R^1 = R^2$ = isopropyl **4.6e**, 52%

R = 4.3a R^1 = H, R^2 = isopropyl **4.6f**, 49%

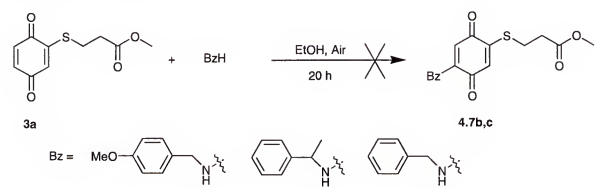
Scheme 4.4

In another case, treatment of the compound **4.3a** with a mixture of *cis* and *trans* of 3,5-dimethylpiperidine produced several products based on TLC and crude ^{1}H NMR and ^{13}C NMR (Scheme 4.5).



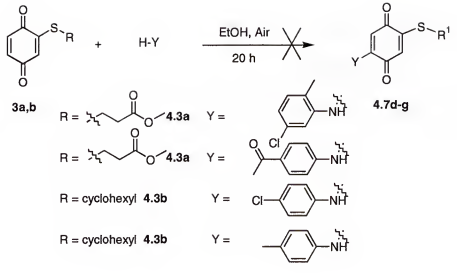
Scheme 4.5

When benzylic amines were used, a myriad of compounds were observed on ^{1}H NMR and ^{13}C NMR. An insoluble crude slurry was obtained in most cases which could be a sign of polimerization (Scheme 4.6).



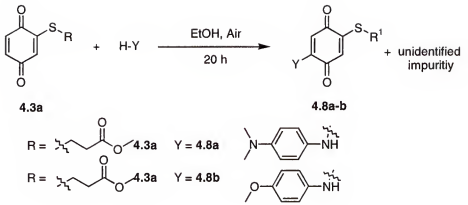
Scheme 4.6

Although we found that the aniline derivatives gave better results than the alkylamines there were a few negative results with anilines bearing either a substitutent at the 4-position or a halogen atom in the ring. In most instances, unidentifiable compounds as well as starting material were recovered (Scheme 4.7).



Scheme 4.7

Treatment of the compound **4.3a** with either N,N-dimethyl-1,4-phenylene-diamine or p-anisidine produced the desired product but both products presented an unidentifiable impurity really hard to separate (Scheme 4.8). After three recrystallizations and several washes with Hex:EtOAc (7:3) which helps to remove the compound **4.3a**, the desired compounds (**4.8a,b**) could not be isolated. Thin layer chromatography showed formation of streaks, thus compounds could not be purified by column chromatography due to decomposition on silica gel.



Scheme 4.8

In conclusion, a straightforward preparation of 2-thio-5-amino substituted benzoquinones by a one-step synthetic addition/oxidation protocol is reported. Initial introduction of a 2-thio substituent affords the corresponding quinones in 40-94% yields. Subsequent introduction of an amino substituent gives the desired 2-thio-5-amino substituted benzoquinones in 70-97% yields. Twelve compounds with a variety both of amino and of thio substituents were prepared. Since this method does not require presence of at least two good leaving groups in the starting quinone, it has a wider scope as well as advantages over some other approaches in regards to the simplicity and availability of the starting materials [55AG217, 57AG252, 57HCA502, 73TL4696, 77MI171].

4.3 Experimental Section

General Procedure for 2-Alkylthiohydrobenzoquinones. *p*-Benzoquinone (10.8 g, 0.1 mole) was dissolved in ethanol (250 mL) and treated with a mercapto derivative (11.06 g, 0.1 mole) under a constant gentle stream of air. The reaction mixture turned orange and was allowed to stir for two days. Then, EtOH was evaporated and the orange slurry was purified by short silica gel column chromatography [Hex: EtOAc (9:1) and (1:1)] to give the product as a crystalline material.

Methyl 3-[(2,5-dihydroxyphenyl)sulfanyl]propanoate (**4.2a**): Yield 98%, orange microcrystals, mp 21–25 °C; ^{1}H NMR δ 8.30 (br s, 1H), 7.24 (br s, 1H), 6.91–6.68 (m, 3H), 3.67 (s, 3H), 3.00 (t, *J* = 7.2 Hz, 2H), 2.60 (t, *J* = 7.2 Hz, 2H); ^{13}C NMR δ 171.9, 150.6, 149.6, 149.5, 120.2, 117.2, 115.7, 115.4, 51.4, 33.7, 29.6. HRMS (FAB) calcd for $C_{10}H_{12}O_4S$ (M+1): 229.0456. Found: 229.0535.

2-Cyclohexylsulfanylhydroquinone (**4.2b**): Yield 78%, orange microcrystals, mp 25–27 °C; ^{1}H NMR δ 6.97–6.96 (d, *J* = 2.9 Hz, 1H), 6.87–6.84 (m, 1H), 6.79–6.75 (pseudo d, *J* = 2.9 Hz, 1H), 6.49 (br s, 1H), 5.90 (br s, 1H), 2.85–2.77 (m, 1H), 1.91–1.87 (m, 2H); 1.74–1.69 (m, 2H), 1.58–1.46 (m, 1H), 1.32–1.17 (m, 5H); ^{13}C NMR δ 151.4, 148.5, 122.6, 118.4, 117.9, 114.8, 48.7, 33.4, 26.0, 25.4. Anal. calcd for $C_{12}H_{16}O_2S$: C, 64.25; H, 7.19. Found: C, 64.33; H, 7.29.

2-Dodecylsulfanylhydroquinone (**4.2c**): Yield 45% (as an inseparable mixture with bis-alkylthio adduct), orange microcrystals, mp 59–61 °C; ^{1}H NMR δ 6.97-6.76 (m, 2H), 6.32 (d, *J* = 5.6 Hz, 1H), 4.88 (br s, 1H), 2.93-2.67 (m, 2H), 2.52 (q, *J* = 7.5 Hz, 1H),

1.74-1.53 (m, 2H), 1.49-1.26 (m, 18H), 0.88 (t, J = 6.2 Hz, 3H); ^{13}C NMR δ 150.9, 148.8, 125.3, 121.5, 118.0, 115.1, 34.0, 31.9, 29.6, 29.5, 29.3, 29.1, 29.0, 28.6, 28.4, 24.6, 22.7, 14.1. HRMS (FAB) calcd for $C_{18}H_{30}O_2S$ (M+1): 311.1966. Found: 311.2045.

General Procedure for 2-Alkylthio-1,4-benzoquinones. To 2.28 g (10.0 mmol) of a 2-thio substituted hydroquinone dissolved in 50 mL of CH_2Cl_2 a solution of $NaIO_4$ (2.14 g, 10.0 mmol) in 10 mL of deionized water was added. Benzyltrimethylammonium bromide (50 mg) was added and the mixture was stirred for 10 minutes. The organic layer was separated, and CH_2Cl_2 was evaporated under reduced pressure. Gradient flash column chromatography using Hex:EtOAc (8:2), (7:3), (1:1) and EtOAc gave crystalline product.

Methyl 3-[(3,6-dioxo-1,4-cyclohexadien-1-yl)-sulfanyl]propanoate (4.3a): Yield 87%, orange needles, mp 91-94 °C; ^{1}H NMR δ 6.84-6.72 (m, 2H), 6.43 (d, J = 2.1 Hz, 1H), 3.74 (s, 3H), 3.08 (t, J = 7.2 Hz, 2H), 2.75 (t, J = 7.1 Hz, 2H); ^{13}C NMR δ 183.8, 183.7, 171.1, 151.8, 137.4, 136.1, 124.9, 52.1, 31.9, 24.9. Anal. calcd for $C_{10}H_{10}O_4S$: C, 53.09; H, 4.45. Found: C, 53.18; H, 4.44.

2-(Cyclohexylsulfanyl)-1,4-benzoquinone (4.3b): Yield 94 %, orange plates, mp = 111-112 °C, lit. mp 102.0-106.0 °C [91JOC5808-15], ^{1}H NMR δ 6.83-6.70 (m, 2H), 6.43 (s, 1H), 3.14-3.09 (m, 1H), 2.07-2.02 (m, 2H), 1.83-1.81 (m, 2H), 1.68-1.66 (m, 1H), 1.57-1.32 (m, 5H); ^{13}C NMR δ 187.1, 184.0, 152.0, 137.2, 136.2, 124.8, 42.5, 31.9, 25.6, 25.4.

2-(Dodecylsulfanyl)-1,4-benzoquinone (4.3c): Yield 40 %, orange plates, mp 79-81 °C; ^{1}H NMR δ 6.82-6.70 (m, 2H), 6.38-6.31 (m, 1H), 2.79-2.65 (m, 2H), 1.75-1.65 (m, 2H),

1.46-1.26 (m, 18H), 0.88 (t, J = 6.2 Hz, 3H); ^{13}C NMR δ 187.2, 183.9, 153.2, 137.4, 136.1, 124.7, 31.8, 30.7, 30.4, 29.6, 29.5, 29.4, 29.3, 29.0, 28.9, 27.2, 22.6, 14.1. Anal. calcd for $C_{18}H_{28}O_2S$: C, 70.07; H, 9.17. Found: C, 69.69; H, 9.48.

General Procedure for 2-Alkylthio-5-Amino-Substituted 1,4-Benzoquinones. The appropriate 2-alkylthio-1,4-benzoquinone (1.99 mmole) was dissolved in ethanol (25 mL) and treated with the corresponding amine (1.99 mmole) under a constant gentle stream of air. The reaction mixture turned dark purple and was stirred for 20 h. The EtOH was evaporated and the purple slurry was recrystallized from hexane and absolute ethanol to give crystalline product.

Methyl 3-{[4-(4-anilinoanilino)-3,6–dioxo-1,4-cyclohexadien-1-yl]sulfanyl} propanoate (**4.4a**): Yield 97%, purple microcrystals, mp 206-208 °C; ^{1}H NMR δ 9.16 (s, 1H), 8.30 (s, 1H), 7.27-7.19 (m, 4H), 7.11-7.09 (m, 4H), 6.84 (t, J = 6.4 Hz, 1H), 6.46 (s, 1H), 5.77 (s, 1H), 3.64 (s, 3H), 3.08 (t, J = 6.2 Hz, 2 H), 2.74 (t, J = 6.6 Hz, 2H); ^{13}C NMR δ 180.7, 179.4, 171.5, 156.5, 145.7, 143.0, 141.4, 129.3, 124.9, 120.7, 120.1, 117.0, 116.9, 97.3, 51.8, 31.7, 24.6. Anal. calcd for $C_{22}H_{20}N_2O_4S$: C, 64.69; H, 4.94; N, 6.86. Found: C, 65.47; H, 4.57; N, 6.96.

2-Anilino-5-(cyclohexylthio)benzo-1,4-quinone (**4.4b**): Yield 77%, brown microcrystals, mp 170-172 °C; ^{1}H NMR δ 7.54 (br s, 1H), 7.40 (t, J = 7.3 Hz, 2H), 7.23 (t, J = 7.8 Hz, 3H), 6.34 (s, 1H), 6.18 (s, 1H), 3.18-3.05 (m, 1H), 2.14-2.02 (m, 2H), 1.90-1.77 (m, 2H), 1.66-1.12 (m, 6H); ^{13}C NMR δ 182.6, 179.4, 158.0, 143.8, 129.6, 125.7, 122.3, 119.9, 116.1, 99.9, 42.8, 31.9, 25.7, 25.5. Anal. calcd for $C_{18}H_{19}NO_2S$: N, 4.47. Found: N, 4.10.

Methyl 3-[(4-anilino-3,6-dioxo-1,4-cyclohexadien-1-yl)sulfanyl]propanoate (4.4c): Yield 90%, purple microcrystals, mp 180-181 °C; ^{1}H NMR δ 7.57 (br s, 1H), 7.40 (t, *J* = 7.8 Hz, 2H), 7.22 (d, *J* = 7.5 Hz, 2H), 6.85 (t, *J* = 8.4 Hz, 1H), 6.35 (s, 1H), 6.17 (s, 1H), 3.74 (s, 3H), 3.07 (t, *J* = 7.2 Hz, 2H), 2.76 (t, *J* = 7.2 Hz, 2H); ^{13}C NMR δ 182.1, 179.3, 171.2, 157.7, 143.8, 137.0, 129.6, 125.8, 122.3, 120.0, 99.7, 52.2, 31.9, 25.2. Anal. calcd for $C_{16}H_{15}NO_4S$: N, 4.41. Found: N, 4.29.

Methyl 3-[(4-morpholino-3,6-dioxo-1,4-cyclohexadien-1-yl)sulfanyl]propanoate (4.4d): Yield 81%, purple microcrystals, mp 125-126 °C; ^{1}H NMR δ 6.18 (s, 1H), 5.75 (s, 1H), 3.88-3.80 (m, 4H), 3.73 (s, 3H), 3.56-3.50 (m, 4H), 3.03 (t, *J* = 7.5 Hz, 2H), 2.73 (t, *J* = 7.2 Hz, 2H); ^{13}C NMR δ 181.8, 180.8, 171.2, 153.8, 152.1, 123.1, 107.3, 66.3, 52.1, 49.0. 32.0, 25.0. Anal. calcd for $C_{14}H_{17}NO_5S$: N, 4.50. Found: N, 4.12.

Methyl 3-[3,6-dioxo-4-(phenethylamino)-1,4-cyclohexadien-1-ylsulfanyl]propanoate (4.4e): Yield 70%, purple microcrystals, mp 137-138 °C; ^{1}H NMR δ 7.36-7.19 (m, 5H), 6.21 (s, 1H), 5.95 (br s, 1H), 5.53 (s, 1H), 3.72 (s, 3H), 3.39 (q, *J* = 6.8 Hz, 2H), 3.03 (t, *J* = 7.6 Hz, 2H), 2.93 (t, *J* = 7.1 Hz, 2H), 2.72 (t, *J* = 7.3 Hz, 2H); ^{13}C NMR δ 180.8, 178.9, 171.2, 158.4, 147.2, 137.5, 128.9, 128.6, 127.0, 119.9, 97.1, 52.1, 43.6, 34.2, 31.9, 25.2. Anal. calcd for $C_{18}H_{19}NO_4S$: C, 62.59; H, 5.54. Found: C, 62.93; H, 5.88.

Methyl 3-[(4-*N*-methylanilino-3,6-dioxo-1,4-cyclohexadien-1-yl)sulfanyl]propanoate (4.4f): Yield 73%, dark red microcrystals, mp 113-115 °C; ^{1}H NMR δ 7.41-7.36 (m, 2H), 7.29-7.10 (m, 1H), 7.08 (d, *J* = 8.5 Hz, 2H), 6.10 (s, 1H), 5.78 (s, 1H), 3.71 (s, 3H), 3.37 (s, 3H), 3.01 (t, *J* = 7.2 Hz, 2H), 2.71 (t, *J* = 7.2 Hz, 2H); ^{13}C NMR δ 181.6, 180.1, 171.2,

154.1, 150.8, 147.2, 129.6, 126.7, 125.3, 122.5, 116.0, 107.3, 52.1, 43.2, 32.0, 25.0. Anal. calcd for $C_{17}H_{17}NO_4S$: C, 61.62; H, 5.17; N, 4.23. Found: C, 61.67; H, 5.15; N, 4.16.

Methyl 3-[4-(2–naphthylamino)-3,6–dioxo-1,4-cyclohexadien-1yl-sulfanyl] propanoate (4.4g): Yield 85%, black microcrystals, mp 166-169 °C; ^{1}H NMR δ 7.87-7.75 (m, 4H), 7.66 (s, 1H), 7.54-7.42 (m, 2H), 7.32-7.27 (m, 1H), 6.36 (s, 1H), 6.34 (s, 1H), 3.74 (s, 3H), 3.07 (t, *J* = 7.3 Hz, 2H), 2.76 (t, *J* = 7.3 Hz, 2H); ^{13}C NMR δ 182.2, 179.2, 171.2, 157.7, 143.5, 134.5, 133.6, 131.0, 129.7, 127.7, 127.5, 127.1, 126.0, 121.2, 120.1, 119.1, 100.0, 52.2, 31.9, 25.2. Anal. calcd for $C_{20}H_{17}NO_4S$: N, 3.81. Found: N, 3.79.

Methyl 3-[4-(4-isopropylanilino)-3,6–dioxo-1,4–cyclohexadien-1-yl-sulfanyl] propanoate (4.4h): Yield 71%, purple microcrystals, mp 135-137 °C; ^{1}H NMR δ 7.53 (br s, 1H), 7.28-7.13 (m, 4H), 6.34 (s, 1H), 6.12 (s, 1H), 3.73 (s, 3H), 3.07 (t, *J* = 7.3 Hz, 2H), 2.91 (septet, *J* = 6.9 Hz, 1H), 2.75 (t, *J* = 7.3 Hz, 2H), 1.25 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR δ 181.9, 179.4, 171.2, 157.9, 146.9, 144.2, 134.6, 127.5, 122.5, 120.0, 99.3, 52.1, 33.6, 31.9, 25.2, 23.9. Anal. calcd for $C_{19}H_{21}NO_4S$: N, 3.90. Found: N, 3.90.

Methyl 3-[4-(2,4-dimethylanilino)-3,6-dioxo-1,4-cyclohexadien-1-yl-sulfanyl] propanoate (4.4i): Yield 92%, red plates, mp 135-137 °C; ^{1}H NMR δ 7.27 (s, 1H), 7.12-7.02 (m, 3H), 6.32 (s, 1H), 5.69 (s, 1H), 3.74 (s, 3H), 3.07 (t, *J* = 7.2 Hz, 2H), 2.75 (t, *J* = 7.3 Hz, 2H), 2.32 (s, 3H), 2.21 (s, 3H); ^{13}C NMR δ 181.7, 179.4, 171.2, 158.0, 145.3, 136.9, 132.7, 132.3, 132.0, 127.6, 124.4, 120.0, 99.0, 52.2, 31.9, 25.2, 20.9, 17.6. Anal. calcd for $C_{18}H_{19}NO_4S$: C, 62.59; H, 5.54; N, 4.05. Found: C, 62.54; H, 5.60; N, 4.12.

Methyl 3-[3,6-dioxo-4-(2-toluidino)-1,4-cyclohexadien-1-yl-sulfanyl]propanoate (4.4j): Yield 75%, red needles, mp 135-138 °C; ^{1}H NMR δ 7.33 (br s, 1H), 7.29-7.18 (m, 4H), 6.34 (s, 1H), 5.75 (s, 1H), 3.74 (s, 3H), 3.07 (t, *J* = 7.3 Hz, 2H), 2.76 (t, *J* = 7.3 Hz, 2H), 2.26 (s, 3H); ^{13}C NMR δ 181.8, 179.3, 171.2, 157.9, 144.9, 135.0, 132.8, 131.3, 127.0, 126.9, 124.3, 120.0, 99.2, 52.1, 31.8, 25.2, 17.6. Anal. calcd for $C_{17}H_{17}NO_4S$: C, 61.62; H, 5.17; N, 4.23. Found: C, 61.92; H, 5.34; N, 4.20.

Methyl 3-[4-(3-methoxyanilino)-3,6–dioxo-1,4-cyclohexadien-1-yl-sulfanyl] propanoate (4.4k): Yield 84%, brown microcrystals, mp 117-120 °C; ^{1}H NMR δ 7.55 (br s, 1H), 7.32-7.27 (m, 1H), 6.82-6.71 (m, 3H), 6.34 (s, 1H), 6.20 (s, 1H), 3.81 (s, 3H), 3.74 (s, 3H), 3.07 (t, *J* = 7.3 Hz, 2H), 2.75 (t, *J* = 7.3 Hz, 2H); ^{13}C NMR δ 182.0, 179.2, 171.2, 160.4, 157.6, 143.7, 138.1, 130.3, 120.0, 114.5, 111.1, 108.2, 100.0, 55.4, 52.2, 31.9, 25.2. Anal. calcd for $C_{17}H_{17}NO_5S$: N, 4.03. Found: N, 3.92.

Methyl 3-[4-(2,3-dihydro-1*H*-indol-1-yl)-3,6-dioxo-1,4-cyclohexadien-1-yl-sulfanyl] propanoate (4.4l): Product was obtained in 76% as a black oil (containing a small amount of hydroquinone derivative) after a silica gel column by eluting with Hex:EtOAc (9:1), (7:3) and (1:1); ^{1}H NMR δ 7.27-7.15 (m, 3H), 7.00 (t, *J* = 7.2 Hz, 1H), 6.51 (s, 1H), 6.27 (s, 1H), 4.25 (t, *J* = 7.6 Hz, 2H), 3.73 (s, 3H), 3.12 (t, *J* = 8.2 Hz, 2H), 3.06 (t, *J* = 7.5 Hz, 2H), 2.75 (t, *J* = 7.3 Hz, 2H); ^{13}C NMR δ 181.9, 180.9, 171.3, 154.4, 146.9, 143.2, 134.3, 127.1, 125.5, 124.0, 122.3, 115.7, 107.4, 54.6, 52.1, 32.0, 29.0, 24.9. Anal. calcd for $C_{18}H_{17}NO_4S$: N, 4.08. Found: N, 3.87.

Methyl 3-(4-[3,4–dihydro-1(2*H*)-quinolinyl]-2,5-dihydroxyphenylsulfanyl)propanoate (4.5a): Product was obtained in 72% as a black oil after a silica gel column by eluting with Hex:EtOAc (9:1), (7:3) and (1:1); ^{1}H NMR δ 7.15 (s, 1H), 7.03 (d, *J* = 7.2 Hz, 1H), 6.92 (pseudo t, *J* = 7.5 Hz, *J* = 1.5 Hz, 1H), 6.82 (s, 1H), 6.73 (pseudo t, *J* = 7.4 Hz, 1H), 6.52 (br s, 1H), 6.28 (d, *J* = 8.1 Hz, 1H), 5.73 (br s, 1H), 3.70 (s, 3H), 3.42 (t, *J* = 5.6 Hz, 2H), 2.98 (t, *J* = 7.1 Hz, 2H), 2.91 (t, *J* = 6.3 Hz, 2H), 2.60 (t, *J* = 7.1 Hz, 2H), 2.14-2.06 (m, 2H); ^{13}C NMR δ 172.1, 151.3, 146.1, 144.2, 137.0, 129.5, 126.8, 123.8, 121.2, 119.1, 116.4, 114.9, 113.0, 51.9, 50.8, 33.9, 31.1, 27.2, 22.5. Anal. calcd for $C_{19}H_{21}NO_4S$: N, 3.90. Found: N, 3.60.

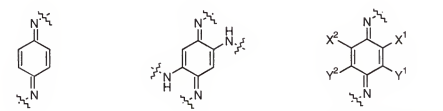
2-(4-Anilinoanilino)-5-(cyclohexylsulfanyl)benzo-1,4-quinone (4.5b): 2-(Cyclohexylsulfanyl)-1,4-benzoquinone (14.84 g, 66.85 mmole) was dissolved in ethanol (200 mL) and treated with *N*-phenyl-1,4-phenylenediamine (12.32 mL, 66.85 mmole) under a constant gentle stream of air. The reaction mixture turned dark purple and was stirred for 20 h. The EtOH was evaporated and the purple slurry was recrystallized from hexane and absolute ethanol to give 2-(4-anilinoanilino)-5-(cyclohexylsulfanyl)-1,4-benzoquinone as black microcrystals (26.47 g, 98%) with mp 221-224 °C. ^{1}H NMR and ^{13}C NMR δ: broad bands, perhaps due to many conformers of **4.5b** coexisting in solution at room temperature. HRMS (FAB) calcd for $C_{24}H_{24}N_2O_2S$ (M): 406.1715. Found: 406.1725.

CHAPTER 5
SYNTHESIS OF A NOVEL CLASS OF BENZOQUINONE DIIMINES

5.1 Introduction

Our recent work on 5-heterosubstituted 2-alkylthio-1,4-benzoquinones as potential rubber additives (from previous Chapter 4) [00JRC01] is extended here to the corresponding 5-heterosubstituted 2-alkylthio-1,4-benzoquinone diimines and 2,5-bis-amino benzoquinone diimines.

Known 1,4-benzoquinone diimines (QDI's) can be classified under three major categories: I, II and III (Scheme 1). Class I compounds contain no substituents attached to the benzoquinoid ring. Class II, the largest group, contains amino-substituents at the 2 and 5 positions of the benzoquinoid ring. Class III comprises all other *p*-benzoquinone diimines.



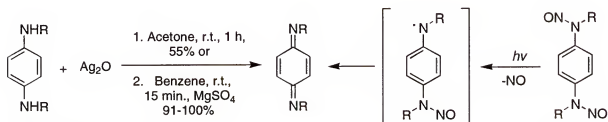
Class I **Class II** **Class III**

Scheme 5.1

5.1.1 Published Preparations of *p*-Benzoquinone Diimines

Many benzoquinone diimines (QDI's) were previously prepared by the oxidation of phenylenediamine derivatives with manganate [81IJC995], ferricyanate [82MI695], iodine [79MI877], silver ion [04CB4605], silver oxide [50JA4601], and lead tetraacetate (or "red lead") [51JA1149].

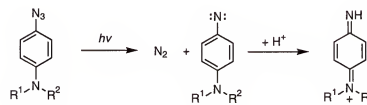
Thus, oxidation of *N,N'*-diphenyl-*p*-phenylenediamine (**5.1a**) with Ag_2O (Scheme 2) gives *N,N'*-diphenyl-*p*-phenylenediimine (**5.2a**) [69T3641]. Oxidation of *N*-(1,3-dimethylbutyl)-*N'*-phenyl-1,4-phenylenediamine (HPPD) (**5.1b**), an effective antiozonant and antioxidant used in rubber industry [86MI159], with Ag_2O gave the corresponding QDI **5.2b** in 55% yield; similar conversion is achieved by photocatalytic oxidation using Ru^{3+} [94JPC2883]. The QDI **5.2a** can be prepared by two consecutive photo cleavages of NO groups from the bis-nitroso derivative of *N,N'*-diphenyl-*p*-phenylenediimine (**5.3**) (Scheme 5.2) [97JA3840].



Scheme 5.2

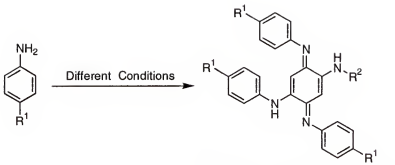
QDI's iminium salts **5.6** can be prepared *in situ* by photolysis of azidoanilines **5.4**, presumably *via* nitrene intermediates **5.5** [77AGE266, 71JA1347] (Scheme 3). Another

approach to the preparation of QDI's iminium dicationic salts in yields of up to 82% is by oxidation of *N,N,N',N'*-tetrasubstituted *p*-phenylenediamines with silver perchlorate [59CB245].



Scheme 5.3

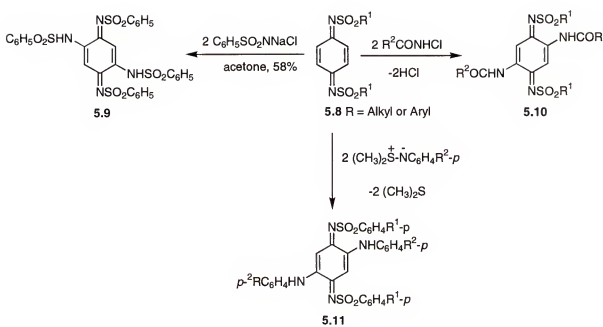
N,N'-Diaryl-2,5-bisarylamino-*p*-benzoquinone diimines or azophenines, which belong to the second class of QDI's and are dyes intermediates [54MI724], have been synthesized by a wide variety of methods many of which involve the separation of mixtures and afford low yields. Parent azophenine (**5.7a**) has been prepared by heating *p*-benzoquinonedianil with aniline [56JCS3814]. Substituted azophenines **5.7b** are also formed in 25-35% yields by oxidizing anilines with 1,1,2,2-tetrachloroethane and hexachloroethane in the presence of copper bronze [84BCJ1405]. The oxidation of aniline by 3- and 4-azidopyridine 1-oxides gives azophenines [84PJC805]. Peroxidaze oxidation of 4-chloroaniline gives 2-amino-5chloroanilinobenzoquinone di-4-chloroanil (**5.7c**) [69T4153]. Benzoquinone diimines form as side products in the decomposition of nitroxide [74JCS(P1)2208]. These reactions are summarized in Scheme 5.4.



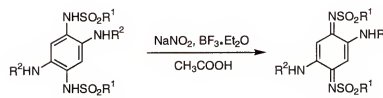
5.7a R^1 = H , R^2 = Ph
5.7b R^1 = *p*-O-Alkyl-Ph , R^2 = *p*-O-Alkyl
5.7c R^1 = *p*-Cl-Ph , R^2 = H
5.7d R^1 = Ph , R^2 = H

Scheme 5.4

N,N'-Bis[phenylsulfonyl]-1,4-benzoquinone diimine (**5.8**) is sulfanylamidated by sodium *N*-chlorobenzenesulfonylchloroamide to form 2,5-bis(phenylsulfonylamino)-*N,N'*-bis(phenylsulfonyl)-1,4-benzoquinone diimine (**5.9**) (Scheme 5) [76ZOR2479]. Similarly, amidation of **5.8** gave the corresponding sulfonyl benzoquinone diimine derivatives (**5.10**) in one step [84ZOR1040, 87ZOR1215]. Arylaminated *N*-arylsulfimides (**5.11**) were reported [86ZOR461] (Scheme 5.5). 1,4-Di(sulfonamido)-benzene were oxidized by nitrosating agents [94ZOR288] (Scheme 5.6).



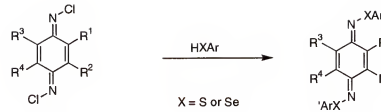
Scheme 5.5



5.12, **5.13**, (a) R^1 = Ph, R^2 = $COCH_3$, (b) $COC_6H_4NO_2$-3, (c) $COOC_2H_5$.

Scheme 5.6

Class III of benzoquinone diimines have the smallest number of published syntheses. Many symmetrical and unsymmetrical *N,N'*-bisarylthio and *N,N'*-bisaryl-seleno-quinone diimines **5.15** have been prepared by treatment of *N,N'*-dichloro quinone diimines **5.14** with thiols and seleno compounds [82JCR(S)138] (Scheme 5.7).

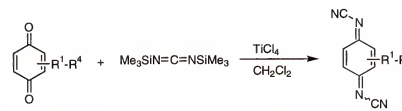


5.14 **5.15**

$R^1 = R^2 = R^3 = R^4 = H$
$R^1 = R^3 = CH_3, R^2 = R^4 = H$
$R^1 = , R^2 = CH{=}CH{-}CH{=}CH, R^3 = R^4 = H$
$R^1 = , R^2 = CH{=}CH{-}CH{=}CH, R^3 = R^4 = CH{=}CH{-}CH{=}CH$

Scheme 5.7

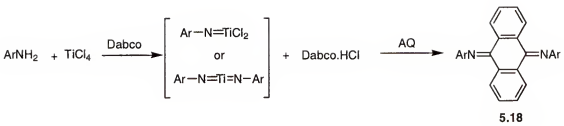
More recently, *N,N'*-dicyanoquinone diimine **5.17** (DCNQI) salts have gained attention due to their high conductivity and ease of synthesis from benzoquinones **5.16** and bis(trimethylsilyl)carbodiimide [84AGE447, 91MI1781] (Scheme 5.8).



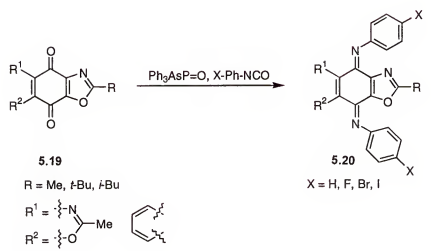
5.16 R^1-R^4 = H, Me, *t*-Bu, OMe, Cl **5.17** 24-84%

Scheme 5.8

A synthetic route to poly(quinone imines) was developed by treatment of anthraquinone (AQ) with aromatic diamines (or aniline as in compound **5.18**) in the presence of $TiCl_4$ *via* a reactive titanium/aniline intermediate [95MI1] (Scheme 5.9).



Scheme 5.9



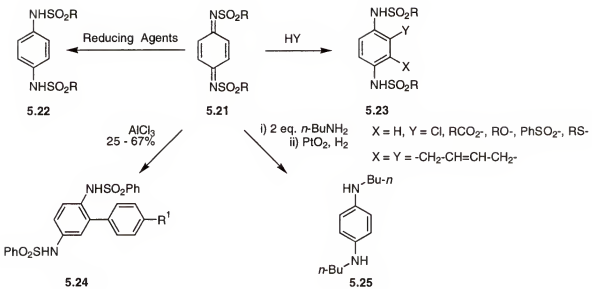
Scheme 5.10

Employing the same model as above, some heterocyclic quinone arylimines were prepared through Wittig addition of triphenylarsinimines to the carbonyl functionality of heterocyclic benzoquinone derivatives. Polyaromatic quinone imines **5.20** are readily formed from triphenylarsine oxide and aryl isocyanates (Scheme 5.10) [95MI9].

5.1.2 Published Reactions of p-Benzoquinone Diimines

Most reactions of *p*-benzoquinone diimines fall into two broad types: reduction and additions. The reactivity of benzoquinone diimines (QDI) is dictated by a strong tendency to form a stable benzenoid structure. Therefore, they are very reactive towards nucleophilic addition and undergo reduction more readily than do quinones. Most published reactions of QDI's relate to studies of the relatively stable diacyl and disulfonyl derivatives [70MI663].

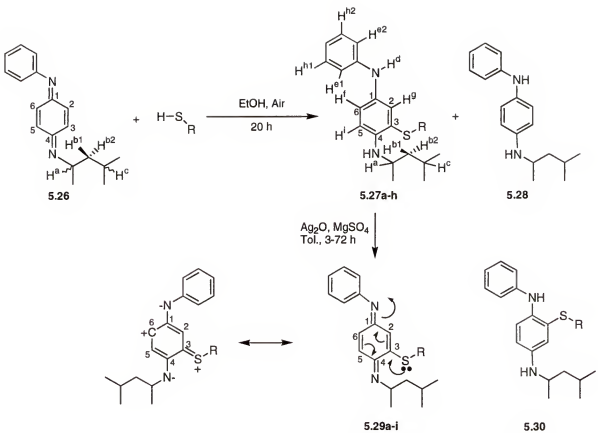
Common reducing agents, such as hydrogen and a catalyst, zinc and acetic acid, hydroiodic acid, reduce *p*-disulfonylquinone diimines **5.21** rapidly and quantitatively to the corresponding sulfonamides **5.22** [70MI663]. A wide variety of compounds has been added to *p*-disulfonyl benzoquinone diimine **5.21** [70MI663], while several aromatic compounds in the presence of aluminum chloride were found to be added presumably by a 1,4-proccess, to benzoquinone *p*-dibenzenesulfonyldiimines [51JA1149]. Aliphatic primary amines seemed to show the ability for 1,2-addition followed by elimination of benzenesulfonamide (compound **5.25**) [70MI663] (Scheme 5.11).



Scheme 5.11

5.2 Results and Discussion

We prepared N^1-(1,3-dimethylbutyl)-2-(alkylsulfanyl)-N^4-phenyl-1,4-benzenediamines **5.27a-h** in 71-93% yields by treatment of *N*-4-[(1,3-dimethylbutyl)imino]-2,5-cyclohexadien-1-ylideneaniline (**5.26**) with mercaptans. Only the single regioisomer was observed in all cases. The assignment of **5.27** rather than **5.30** is justified below. The synthetic results are summarized in Table 5.1. Compound **5.28** (the reduced form of product **5.26**), was obtained as a by-product (4-14%) (Scheme 5.12).



For designation of R in **5.27** and **5.29**, see Tables 5.1 and 5.2

Scheme 5.12

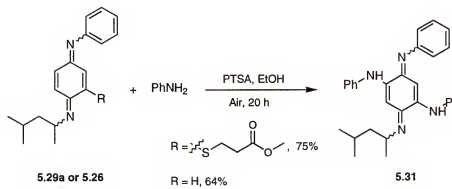
In the ^{1}H NMR spectrum of **5.26**, protons H^{b1}, H^{b2}, and H^c are showed as a multiplet at 1.67-1.38 ppm. Proton H^c showed as a multiplet at 4.07-3.94 ppm (Scheme 5.12). That the thiol group at the C-3 position of QDI **5.26** to give compounds **5.27a-h** is supported by the fact that protons H^{b1}, H^{b2}, and H^c split into three separate multiplets at 1.82-1.52 ppm, 1.51-1.36 ppm, and 1.30-1.16 ppm, and the H^a proton is a multiplet at 3.54-3.42 ppm. Free rotation around the C-4 of the N-C bond in **5.27a-h** (in contrast to the rigid E/Z conformation for N=C at C-4 in compound **5.26**) the thiol group at C-3 in the benzenediamine ring creates a new environment for protons H^{b1}, H^{b2}, and H^c resulting

in three different chemical shifts. Besides showing the characteristic ^{13}C NMR signals for the two N-C bonds for the benzenediamine groups at 145.9- 142.4 ppm, compounds **5.27a-h** showed the newly formed quaternary carbon at C-3 with a chemical shift around 128.0-122.1 ppm when an alkyl group was attached to the sulfur atom and 135.7-131.2 ppm for the heterocyclic derivatives respectively. Thus the NMR data seems consistent in all cases.

NOE experiments were performed on **5.27a**. When the anilino NH^d proton was irradiated, it produced NOE effects on protons H^{e1} (8.2%), H^{e2} (8.2%), H^f (7.1%) and H^g (7.1%) (Scheme 5.12). Similarly, irradiation of proton H^{e1}, H^{e2} produced NOE effects on protons H^d (5.0%), H^{h1} (8.1%) and H^{h2} (8.1%) respectively. COSY and Hetcor experiments also support the structural configuration of compound **5.27a**. There is correlation between the H^g proton (shown in the ^1H NMR as a doublet) and the H^f proton (shown in the ^1H NMR as a doublet of doublets). COSY and Hetcor Analysis of the compound **5.27a** also present correlation between protons H^f and H^i. These results also confirmed our proposed structure for compound **5.27a**. Thus, addition of the thiol nucleophile occurs at the C-3 position in compounds **5.27a-h** rather than **5.30**.

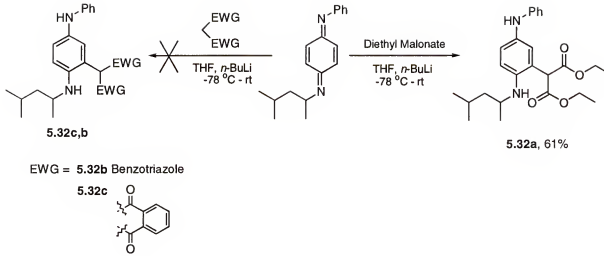
Several attempts using different reaction conditions failed to introduce a second sulfur nucleophile into compounds **5.29a-h**; recovery of starting materials took place in most cases. Two factors could contribute to the lack of reactivity of **5.29**. The thiol group in compounds **5.29a-h** does not produce a strong electron inductive effect at the 6-position (C-6) of benzoquinone diimine in **5.29** because the *N*-alkyl group of **5.27a-h** is not an electron acceptor (Scheme 5.12). Addition at C-5 is not favorable due to steric effects with the *N*-alkyl group of **5.27a-h**.

Addition of Nitrogen Nucleophiles. When compound **5.29a** was treated with an equivalent amount of aniline in the presence of a catalytic amount of p-toluenesulfonic acid, double addition of aniline followed by oxidation formed compound **5.31** in 75% yield (Scheme 5.13). We attempted changing the order of addition of the reagents to introduce the amino group first and the thiol group second. However, when this procedure was applied to compound **5.26** it gave compound **5.31** in 64% yield.



Scheme 5.13

Addition of Carbon Nucleophiles. We made a preliminary exploration of the reactions involving compound **5.26** with stabilized carbanions (Michael addition type). Treatment of **5.26** with the lithium salt of diethyl malonate gave **5.32a** in 61% yield. However, the reaction of **5.26** with 1-(1*H*-1,2,3-benzotriazol-1-ylmethyl)-1*H*-1,2,3-benzotriazole gave recovered **5.26** and its reduction product **5.28**. The lithium salt of 1*H*-indene-1,3(2*H*)-dione apparently adds to **5.26** to give the desired product **5.32c** as shown by ^{1}H and ^{13}C NMR but **5.32c** was not separated from several by-products (Scheme 5.14).



Scheme 5.14

Compounds **5.27a-h** were oxidized to compounds **5.29a-h** by treatment with Ag_2O resulting in yields of 80-99% (Scheme 5.12 and Table 5.2). Purification of the reduced form of compound **5.29i** proved to be difficult. Compound **5.29i** could only be obtained in 55% yield after treatment of the crude product of the diamine derivative with Ag_2O.

Table 5.1

N^1-(1,3-Dimethylbutyl)-2-(sulfanyl-substituted)-N^4-phenyl-1,4-benzenediamine

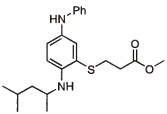
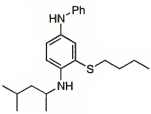
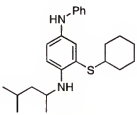
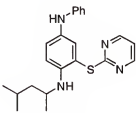
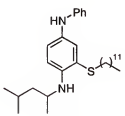
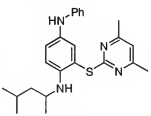
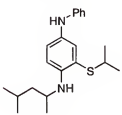
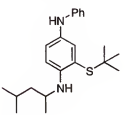
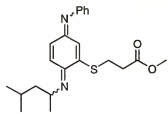
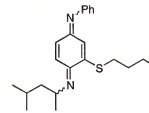
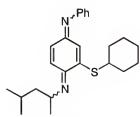
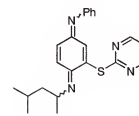
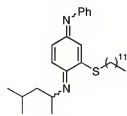
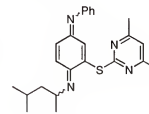
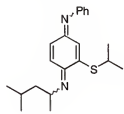
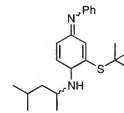
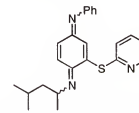
#	Compound	Yield	#	Compound	Yield
5.27a		90%	**5.27e**		76%
5.27b		81%	**5.27f**		71%
5.27c		93%	**5.27g**		87%
5.27d		74%	**5.27h**		85%

Table 5.2

N-3-(Thio-substituted)-4-[(1,3-dimethylbutyl)imino]-2,5-cyclohexadien-1-ylideneaniline

#	Compound	Yield	#	Compound	Yield
5.29a		99%	**5.29e**		96%
5.29b		88%	**5.29f**		80%
5.29c		95%	**5.29g**		98%
5.29d		99%	**5.29h**		97%
			5.29i		55%

The UV spectra of all the 1,4-benzenediamines **5.27a-h** and BQI's **5.29a-i** were taken in acetonitrile on Spectral Instruments 440 Fiber Optic Spectrophotometer. As expected the introduction of the heteroatom substituents results in a bathochromic shift of all absorptions, especially the second $\pi \rightarrow \pi^*$ transition [87MI29-26]. This can be explained by redistribution of the electron density in the molecule caused by the presence of strong electron donating substituents. For the 1,4-benzenediamines **5.27a-h**, the wavelengths and intensities (reported in Table 5.3) of the principal maxima were as follows: 208-217 nm ($1259 < \varepsilon < 2285$), 239-255 nm ($1270 < \varepsilon < 2379$), 274-295 nm ($3792 < \varepsilon < 2271$), 353-391 nm ($541 < \varepsilon < 575$). Subsequent oxidation of compounds **5.27a-h** resulted in a significant bathochromic shift of the second transition to the 290-300 nm ($5113 < \varepsilon < 24253$) range, as well as in an increase in the absorption coefficients (Table 5.3) [87MI29-26].

Table 5.3

UV-Visible Spectra Maxima

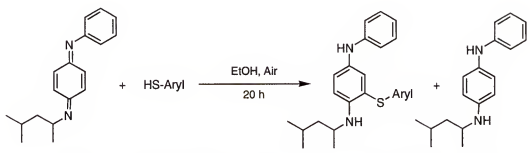
Compound	Concentration	Wavelengths	Absorbance	Absortivity Coefficients
5.27a	1.00E-05	242	0.2058	2.06E+04
	1.00E-05	292	0.1617	1.62E+04
5.27b	1.00E-05	211	0.1956	1.96E+04
	1.00E-05	239	0.127	1.27E+04
	1.00E-05	251	0.1379	1.38E+04
	1.00E-05	294	0.1594	1.59E+04
5.27c	1.00E-05	208	0.1259	1.26E+04
	1.00E-05	244	0.148	1.48E+04
	1.00E-05	275	0.12	1.20E+04
	1.00E-05	292	0.1299	1.30E+04
5.27d	1.00E-05	208	0.3328	3.33E+04
	1.00E-05	254	0.1758	1.76E+04
	1.00E-05	293	0.2342	2.34E+04
5.27e	1.00E-05	254	0.3423	3.42E+04
	1.00E-05	274	0.3792	3.79E+04
5.27f	1.00E-05	210	0.2287	2.29E+04
	1.00E-05	248	0.182	1.82E+04
	1.00E-05	290	0.1982	1.98E+04
	1.00E-05	365	0.0254	2.54E+03
5.27g	1.00E-05	210	0.2663	2.66E+04
	1.00E-05	255	0.2379	2.38E+04
	1.00E-05	290	0.1976	1.98E+04
	1.00E-05	353	0.0541	5.41E+03
5.27h	1.00E-05	217	0.2285	2.29E+04
	1.00E-05	295	0.2271	2.27E+04
	1.00E-05	355	0.0482	4.82E+03
5.29a	1.00E-05	237	0.1357	1.36E+04
	1.00E-05	293	0.3372	3.37E+04
	1.00E-05	391	0.0575	5.75E+03

Table 5.3--continued.

Compound	Concentration	Wavelengths	Absorbance	Absortivity Coefficients
5.29b	1.00E-05	223	0.266	2.66E+04
	1.00E-05	299	0.3935	3.94E+04
	1.00E-05	399	0.0866	8.66E+03
5.29c	1.00E-05	239	0.1377	1.38E+04
	1.00E-05	293	0.3396	3.40E+04
	1.00E-05	393	0.0702	7.02E+03
5.29d	1.00E-04	223	1.6249	1.62E+04
	1.00E-04	300	2.4253	2.43E+04
	1.00E-04	398	0.4877	4.88E+03
5.29e	1.00E-05	224	2.0051	2.01E+05
	1.00E-05	270	0.6784	6.78E+04
5.29f	1.00E-05	256	0.3343	3.34E+04
	1.00E-05	290	0.5113	5.11E+04
	1.00E-05	437	0.0428	4.28E+03
5.29g	1.00E-05	229	0.0875	8.75E+03
	1.00E-05	298	0.3452	3.45E+04
	1.00E-05	380	0.0431	4.31E+03
5.29h	1.00E-05	205	0.0504	5.04E+03
	1.00E-05	236	0.0593	5.93E+03
	1.00E-05	299	0.2671	2.67E+04
	1.00E-05	385	0.0134	1.34E+03
5.29i	1.00E-05	242	0.1244	1.24E+04
	1.00E-05	296	0.3202	3.20E+04
	1.00E-05	385	0.0417	4.17E+03

5.2.1 Unsuccessful Attempts

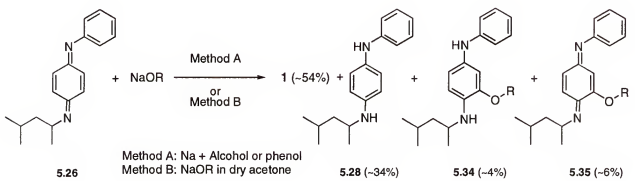
When the compound **5.26** was treated with arylthiol derivatives such as 4-methoxythiophenol, *p*-thiocresol, 4-chlorothiophenol, and 2-naphthalenethiol, the desired products of addition **5.33a-d** were obtained in all cases but they were accompanied by an inseparable amount of the diamine **5.28** which is the reduced form of compound **5.26** (Scheme 5.15).



Scheme 5.15

Addition of Oxygen Nucleophiles. Our last group of nucleophiles employed for the synthesis of novel benzoquinone diimine derivatives was those containing oxygen atoms. We were trying to find suitable conditions for the reaction of the compound **5.26** with alkoxides and phenoxide anions. Our first attempt included the in situ formation of methoxy, ethoxy and phenoxy anions by dissolving Na in a solution of the corresponding alcohol or phenol. GCMS traces showed that the desired compounds **5.34** and **5.35** were produced in very little amounts and that the major compounds recovered were starting

material compound **5.26** and its reduced form **5.28** (Scheme 5.16). These results suggested that we needed to use an aprotic polar solvent such as acetone or acetonitrile. Our next attempt involved the use of pure acetone as solvent and stepwise formation of the corresponding dry alkoxide from its alcohol source. However, similar results were obtained, thus acetone showed that it is also a proton source since large amounts of compound **5.28** were recovered.



Scheme 5.16

In conclusion, an efficient preparation of 2-alkylthio- and 2-aryl(heteroyl)thio-substituted benzoquinone diimines (BQI) is reported. Initial introduction of a 2-thio substituent affords the corresponding 2-thio-substituted 1,4-benzenediamines in 71-93% yields. Subsequent oxidation with Ag_2O gives the desired 2-thio-substituted BQI's in quantitative yields. The latter represent a new class of BQI's in which the benzoquinoid ring has three different groups attached: an alkylimino, a phenylimino and a thio group. A significant advantage of this method is the preferred regioselective attack of the mercaptan nucleophile at the C-3 position due to the electron acceptor ability of the *N*-phenyl group at the C-1 position.

5.3 Experimental Section

General Procedure for the Preparation of N^1-(1,3-dimethylbutyl)-2-(sulfanyl-substituted)-N^4-phenyl-1,4-benzenediamine. *N*-(1,3-Dimethylbutyl)-*N'*-phenyl-p-quinone diimine (0.80 g, 3.0 mmol) was dissolved in ethanol (25 mL) and treated with a mercapto derivative (0.33 mL, 3.0 mmol) under a constant gentle stream of air. The dark reaction mixture was allowed to stirred for 20 h. The solvent was evaporated and the dark brown slurry was purified by silica gel column chromatography [Hex: EtOAc (9:1), (7:3) and (1:1)] to give the corresponding N^1-(1,3-dimethylbutyl)-2-(alkylsulfanyl)-N^4-phenyl-1,4-benzenediamines.

Methyl 3-(5-Anilino-2-[(1,3-dimethylbutyl)amino]phenylsulfanyl)propanoate (**5.27a**): Yield 90%, yellow oil; ^{1}H NMR δ 7.20–7.12 (m, 3H), 6.89 (dd, J = 8.7 Hz, J = 1.0 Hz, 2H), 6.81–6.76 (m, 1H), 6.70 (d, J = 2.7 Hz, 1H), 6.47 (dd, J = 8.7 Hz, J = 2.7 Hz, 1H), 6.06 (s, 1H), 3.59 (s, 3H), 3.44 (m, 1H), 3.25 (br s, 1H), 2.96 (t, J = 7.1 Hz, 2H), 2.53 (t, J = 7.1 Hz, 2H), 1.74 (septet, J = 6.6 Hz, 1H), 1.49–1.42 (m, 1H), 1.40–1.16 (m, 1H), 1.13 (d, J = 6.1 Hz, 3H), 0.94–0.89 (m, 6H); ^{13}C NMR δ 171.9, 144.9, 143.1, 133.2, 129.0, 125.9, 121.7, 119.2, 117.7, 115.7, 113.9, 51.4, 46.7, 46.5, 33.7, 29.1, 24.8, 22.7, 22.3, 20.8. Anal. Calcd for $C_{22}H_{30}N_2O_2S$: N, 7.25. Found: N, 7.53.

2-(Cyclohexylsulfanyl)-N^1-(1,3-dimethylbutyl)-N^4-phenyl-1,4-benzenediamine (**5.27b**): Yield 81%, yellow oil; ^{1}H NMR δ 7.22–7.15 (m, 3H), 6.96 (d, J = 7.6 Hz, 2H), 6.84– 6.77 (m, 2H), 6.50 (dd, J = 8.6 Hz, J = 2.7 Hz, 1H), 6.28 (s, 1H), 3.45 (sectet, J = 6.6 Hz, 1H), 3.14 (bs, 1H), 2.88–2.85 (m, 1H), 1.92–1.88 (m, 2H), 1.77–1.68 (m, 3H),

1.52–1.41 (m, 2H), 1.35–1.18 (m, 6H), 1.14 (d, J = 6.1 Hz, 3H), 0.95–0.90 (m, 6H); ^{13}C NMR δ 144.9, 142.4, 134.8, 129.1, 124.6, 120.3, 120.2 119.6, 116.2, 114.5, 47.1, 47.0, 46.7, 33.3, 25.9, 25.6, 25.0, 22.9, 22.5, 20.9. Anal. Calcd for $C_{24}H_{34}N_2S$: N, 7.32. Found: N, 7.19.

N^1-(1,3-Dimethylbutyl)-2-(dodecylsulfanyl)-N^4-phenyl-1,4-benzenediamine (**5.27c**): Yield 93%, yellow oil; ^{1}H NMR δ 7.20–7.12 (m, 3H), 6.90–6.88 (m, 2H), 6.81–6.69 (m, 1H), 6.68 (s, 1H), 6.47–6.44 (m, 1H), 5.94 (s, 1H), 3.50–3.43 (m, 1H), 3.18 (br s, 1H), 2.71 (t, J = 7.8 Hz, 2H), 1.55 (septet, J = 6.4 Hz, 1H), 1.46–1.42 (m, 3H), 1.30–1.14 (m, 22H), 0.95–0.86 (m, 9H); ^{13}C NMR δ 145.3, 143.3, 132.8, 129.1, 122.1, 119.2, 116.9, 115.6, 113.2, 47.0, 46.8, 34.3, 31.9, 29.6, 29.5, 29.4, 29.3, 29.2, 29.1, 28.7, 25.0, 22.9, 22.6, 22.5, 24.0, 14.1. Anal. Calcd for $C_{30}H_{48}N_2S$: N, 5.98. Found: N, 6.20.

N^1-(1,3-Dimethylbutyl)-2-(isopropylsulfanyl)-N^4-phenyl-1,4-benzenediamine (**5.27d**): Yield 74%, orange oil; ^{1}H NMR δ 7.23–7.16 (m, 3H), 6.98–6.95 (m, 2H), 6.85–6.76 (m, 2H), 6.52 (dd, J = 8.7 Hz, J = 2.8 Hz, 1H), 6.26 (s, 1H), 3.49–3.43 (m, 1H), 3.21–3.10 (m, 2H), 1.80–1.71 (m, 1H), 1.51–1.42 (m, 1H), 1.30–1.25 (m, 1H), 1.23 (d, J = 6.6 Hz, 6H), 1.15 (d, J = 6.2 Hz, 3H), 0.95–0.90 (m, 6H); ^{13}C NMR δ 144.8, 142.5, 134.7, 129.1, 125.1, 120.4, 120.1, 119.6, 116.2, 114.7, 47.1, 46.8, 38.7, 25.0, 23.2, 23.0, 2.5, 21.0. Anal. Calcd for $C_{21}H_{30}N_2S$: N, 8.18. Found: N, 8.50.

***N*-[4-Anilino-2-(butylsulfanyl)phenyl]-*N*-(1,3-dimethylbutyl)amine** (**5.27e**): Yield 76%, orange oil; ^{1}H NMR δ 7.37–7.12 (m, 3H), 6.90 (d, J = 8.4 Hz, 2H), 6.80 (t, J = 7.2 Hz, 1H), 6.69 (d, J = 2.3 Hz, 1H), 6.46 (dd, J = 8.5 Hz, J = 2.5 Hz, 1H), 5.94(s, 1H), 3.50–3.44 (m, 1H), 3.42 (br s, 1H), 2.73 (t, J = 7.2 Hz, 2H), 1.82–1.69 (m, 1H), 1.60–

1.19 (m, 6H), 1.16 (d, J = 6.2 Hz, 3H), 0.93 (t, J = 7.2 Hz, 6H), 0.84 (t, J = 7.3 Hz, 3H); ^{13}C NMR δ 145.4, 143.3, 132.8, 129.1, 128.4, 122.1, 119.3, 116.9, 115.6, 113.2, 47.0, 46.8, 34.0, 31.3, 25.0, 22.5, 21.9 21.0, 13.6. Anal. Calcd for $C_{22}H_{32}N_2S$: N, 7.86. Found: N, 7.76.

N^1-(1,3-Dimethylbutyl)-N^4-phenyl-2-(2-pyrimidinylsulfanyl)-1,4-benzenediamine (5.27f): Yield 71%, brown microcrystals, mp 103–106 °C; ^{1}H NMR δ 8.44 (d, J = 4.8 Hz, 2H), 7.30 (d, J = 4.8 Hz, 1H), 7.14–7.10 (m, 3H), 6.92 (d, J = 4.8 Hz, 1H), 6.82–6.81 (m, 2H), 6.75–6.67 (m, 2H), 5.55(s, 1H), 4.43 (br s, 1H), 3.54–3.47 (m, 1H), 1.61–1.52 (m, 1H), 1.45–1.36 (m, 1H), 1.27–1.13 (m, 1H), 1.11 (d, J = 6.3 Hz, 3H), 0.84 (dd, J = 6.6 Hz, J = 1.8 Hz, 6H); ^{13}C NMR δ 171.7, 157.5, 145.8, 145.5, 131.7, 129.0, 128.9, 126.6, 118.4, 117.0, 114.6, 112.0, 111.7, 46.7, 46.5, 24.8, 22.7, 21.5, 20.9. Anal. Calcd for $C_{22}H_{26}N_4S$: N, 14.77. Found: N, 14.37.

N^1-(1,3-Dimethylbutyl)-2-[(4,6-dimethyl-2-pyrimidinyl)sulfanyl]-N^4-phenyl-1,4-benzenediamine (5.27g): Yield 87%, brown microcrystals, mp 88–91 °C; ^{1}H NMR δ 7.30 (d, J = 8.7 Hz, 1H), 7.14 (t, J = 8.1 Hz, 2H), 6.95 (d, J = 2.6 Hz, 1H), 6.82 (d, J = 4.8 Hz, 2H), 6.75 (t, J = 7.3 Hz, 1H), 6.68–6.645.55 (m, 2H), 6.49 (br s, 1H), 3.52–3.46 (m, 1H), 3.30 (br s, 1H), 2.33 (s, 6H), 1.81–1.72 (m, 1H), 1.52–1.43 (m, 1H), 1.32–1.23 (m, 1H), 1.17 (d, J = 6.2 Hz, 3H), 0.94 (pseudo t, J = 6.2 Hz, 6H); ^{13}C NMR δ 170.8, 167.4, 145.3, 143.1, 135.7, 128.9, 122.7, 122.4, 120.5, 118.9, 116.3, 115.9, 115.7, 46.9, 46.8, 25.0, 23.7, 22.9, 22.5, 21.0. Anal. Calcd for $C_{24}H_{30}N_4S$: N, 13.78. Found: N, 13.83.

2-(*tert*-Butylsulfanyl)-N^1-(1,3-dimethylbutyl)-N^4-phenyl-1,4-benzenediamine (5.27h): Yield 85%, orange oil; ^{1}H NMR δ 7.20 (t, *J* = 8.4 Hz, 3H), 7.03 (d, *J* = 7.9 Hz, 2H), 6.89–6.81 (m, 2H), 6.72 (br s, 1H), 6.59 (d, *J* = 6.7 Hz, 1H), 3.48–3.42 (m, 1H), 3.02 (br s, 1H), 1.83–1.69 (m, 1H), 1.52–1.45 (m, 1H), 1.30–1.24 (m, 10H), 1.15 (d, *J* = 6.2 Hz, 3H), 0.93 (pseudo t, *J* = 7.2 Hz, 6H); ^{13}C NMR δ 144.2, 141.4, 136.7, 129.1, 123.7, 121.0, 119.8, 118.7, 116.6, 116.3, 47.2, 47.0, 46.7, 31.1, 31.0, 24.9, 22.9, 22.5, 22.4, 21.0, 14.0. Anal. Calcd for $C_{22}H_{32}N_2S$: N, 7.86. Found: N, 7.72.

General Procedure for the Preparation of *N*-3-(thio-substituted)-4-[(1,3-dimethylbutyl)imino]-2,5-cyclohexadien-1-ylideneaniline. The corresponding 1,4-benzenediamine (3.02 mmol) was dissolved in 10 ml of toluene and treated with Ag_2O (6.04 mmol) and $MgSO_4$ (8.46 mmol) for 20 h. The orange slurry was filtered (Celite), evaporated and purified by a short silica gel column chromatography [Hex: EtOAc (9:1) and (1:1)] to give the *N*-3-(thio-substituted)-4-[(1,3-dimethylbutyl)imino]-2,5-cyclohexadien-1-ylideneaniline as a mixture of stereoisomers.

Methyl 3- [6- [(1,3-dimethylbutyl)imino] -3- (phenylimino)-1,4-cyclohexadien -1-yl]sulfanylpropanoate (5.29a): Yield 99% (as a mixture of stereoisomers), orange oil; ^{1}H NMR δ 7.34 (t, *J* = 6.1 Hz, 2H), 7.13 (t, *J* = 7.1 Hz, 1H), 6.98–6.83 (m, 3H), 6.75–6.40 (m, 2H), 4.12–3.98 (m, 1H), 3.72 (s, 3H), 3.13 (t, *J* = 6.8 Hz, 2H), 2.78 (pseudo t, *J* = 7.6 Hz, 2H), 1.66–1.40 (m, 3 H), 1.30–1.16 (m, 3H), 0.97–0.82 (m, 6H) ; ^{13}C NMR δ 171.4, 171.3, 156.2, 156.0, 155.9, 155.1, 149.1, 149.0, 146.9, 142.9, 138.1, 128.6, 128.5, 128.0, 124.5, 124.4, 124.1, 122.3, 120.7, 120.1, 120.0, 112.4, 53.7, 53.6, 51.7, 51.6, 47.3,

47.2, 32.3, 32.0, 31.2, 24.9, 24.8, 24.7, 22.9, 22.8, 22.5, 22.3, 22.2, 21.9, 21.7, 13.8. Anal. Calcd for $C_{22}H_{28}N_2O_2S$: N, 7.28. Found: N, 6.79.

***N*-3-(Cyclohexylsulfanyl)-4-[(1,3-dimethylbutyl)imino]-2,5-cyclohexadien-1-ylidene-aniline (5.29b)**: Yield 88% (as a mixture of stereoisomers), orange oil; ^{1}H NMR δ 7.37–7.26 (m, 2H), 7.13 (pseudo t, *J* = 6.4 Hz, 1H), 6.95–6.84 (m, 3H), 6.73–6.64 (m, 2H), 4.03–3.99 (m, 1H), 3.26–3.13 (m, 1H), 2.20–2.00 (m, 2H), 1.90–1.82 (m, 2H), 1.68–1.25 (m, 9H), 1.23–1.18 (m, 3H), 0.98–0.82 (m, 6H); ^{13}C NMR δ 157.0, 156.5, 155.6, 149.5, 147.2, 146.8, 138.1, 128.8, 128.3, 124.6, 122.9, 120.9, 120.4, 120.4, 113.1, 53.9, 53.8, 47.5, 47.4, 42.3, 41.5, 32.7, 32.4, 32.3, 25.9, 25.7, 25.1, 23.2, 23.0, 22.8, 22.4, 22.1. Anal. Calcd for $C_{24}H_{32}N_2S$: N, 7.36. Found: N, 6.94.

***N*-[4-[(1,3-Dimethylbutyl)imino]-3-(dodecylsulfanyl)-2,5-cyclohexadien-1-ylidene]-aniline (5.29c)**: Yield 88% (as a mixture of stereoisomers), orange oil; ^{1}H NMR δ 7.34 (t, *J* = 7.8 Hz, 2H), 7.13 (t, *J* = 7.3 Hz, 1H), 6.86 (dd, *J* = 8.4, 1.2 Hz, 2H), 6.75–6.60 (m, 3H), 4.06–4.01 (m, 1H), 2.87–2.81 (m, 2H), 1.84–1.64 (m, 2H), 1.63–1.39 (m, 5H), 1.30–1.22 (m, 19H), 0.94–0.83 (m, 9H); ^{13}C NMR δ 156.8, 156.5, 156.3, 155.5, 149.7, 149.4, 148.2, 144.3, 138.2, 136.4, 129.4, 128.7, 128.1, 124.6, 124.4, 122.7, 121.2, 120.9, 120.3, 112.4, 53.9, 53.8, 47.5, 31.9, 30.5, 29.6, 29.5, 29.3, 27.6, 25.1, 23.1, 22.8, 22.6, 22.4, 22.3, 22.1, 14.1. Anal. Calcd for $C_{30}H_{46}N_2S$: N, 6.00. Found: N, 6.27.

***N*-[4-[(1,3-Dimethylbutyl)imino]-3-(isopropylsulfanyl)-2,5-cyclohexadien-1-ylidene]-aniline (5.29d)**: Yield 99% (as a mixture of stereoisomers), orange oil; ^{1}H NMR δ 7.34 (t, *J* = 7.8 Hz, 2H), 7.18–7.11 (m, 1H), 6.96–6.83 (m, 3H), 6.74–6.66 (m, 2H), 4.07–4.00 (m, 1H), 3.47–3.36 (m, 1H), 1.63–1.18 (m, 9H), 1.24–1.18 (m, 3H), 0.94–0.82 (m, 6H);

^{13}C NMR δ 156.9, 156.3, 155.6, 149.4, 147.1, 143.2, 138.1, 128.7, 124.6, 122.8, 120.9, 120.3, 113.4, 54.0, 53.8, 47.5, 33.5, 25.1, 23.1, 22.8, 22.7, 22.5, 22.3, 22.2. Anal. Calcd for $C_{21}H_{28}N_2S$: C, 74.07, H, 8.31, N, 8.23. Found: C, 73.72, H, 8.71, N, 8.15.

***N*-3-(Butylsulfanyl)-4-[(1,3-dimethylbutyl)imino]-2,5-cyclohexadien-1-ylidene-aniline(5.29e)**: Yield 99% (as a mixture of stereoisomers), orange oil; ^{1}H NMR δ 7.34–7.29 (m, 2H), 7.10 (t, *J* = 7.3 Hz, 1H), 6.95–6.82 (m, 2H), 6.78–6.62 (m, 3H), 4.09–3.94 (m, 1H), 2.87–2.79 (m, 2H), 1.82–1.69 (m, 2H), 1.65–1.38 (m, 5H), 1.23 (d, *J* = 6.3 Hz, 3H, major isomer), 1.18 (d, *J* = 6.2 Hz, minor isomer), 0.97–0.82 (m, 9H); ^{13}C NMR δ 156.3, 156.0, 155.9, 155.1, 149.1, 149.0, 147.9, 144.0, 137.8, 128.4, 127.6, 124.2, 124.0, 122.2, 120.5, 120.0, 119.9, 112.0, 53.5, 53.3, 47.2, 47.2, 29.8, 29.3, 24.7, 22.9, 22.8, 22.5, 22.1, 21.9, 21.7, 13.3. Anal. Calcd for $C_{22}H_{30}N_2S$: C, 74.51, H, 8.54, N, 7.90. Found: C, 74.85, H, 8.88, N, 8.26.

***N*-[4-[(1,3-Dimethylbutyl)imino]-3-(2-pyrimidinylsulfanyl)-2,5-cyclohexadien-1-ylidene]aniline (5.29f)**: Yield 80% (as a mixture of stereoisomers), orange oil; ^{1}H NMR δ 8.57(d, *J* = 4.8 Hz, 1H), 8.44 (d, *J* = 4.8 Hz, 1H), 7.64 (dd, *J* = 14.0 Hz, *J* = 2.5 Hz, 1H), 7.38–7.30 (m, 2H), 7.18–7.11 (m, 2H), 7.06–6.85 (m, 4H), 4.06–3.95 (m, 1H), 1.58–1.48 (m, 1H), 1.40–1.25 (m, 2H), 1.11–1.05 (m, 3H), 0.85–0.75 (m, 6H); ^{13}C NMR δ 171.5, 171.2, 158.3, 157.9, 157.7, 154.2, 154.0, 150.5, 144.5, 142.3, 136.2, 135.9, 129.3, 129.1, 125.3, 124.2, 123.8, 12.9, 122.5, 121.4, 121.0, 118.2, 118.1, 54.6, 54.5, 47.7, 25.5, 25.4, 23.8, 22.8, 22.7, 22.5, 22.4. Anal. Calcd for $C_{22}H_{24}N_4S$: N, 14.88. Found: N, 14.51.

***N*-4-[(1,3-Dimethylbutyl)imino]-3-[(4,6-dimethyl-2-pyrimidinyl)sulfanyl]-2,5-cyclohexadien-1-ylideneaniline (5.29g)**: Yield 98% (as a mixture of stereoisomers), orange mycrocrystals, mp 112-114 °C; ^{1}H NMR δ 8.13 (s, 1H), 7.33 (t, *J* = 7.8 Hz, 2H), 7.11 (t, *J* = 8.4 Hz, 1H), 6.80 (d, *J* = 8.9 Hz, 2H), 6.77–6.75 (m, 3H), 4.08–4.01 (m, 1H), 2.44 (s, 6H), 1.70–1.39 (m, 3H), 1.21 (d, *J* = 6.3 Hz, 3H), 0.89 (d, *J* = 6.3 Hz, 3H), 0.85 (d , *J* = 6.3 Hz, 3H); ^{13}C NMR δ 169.2, 167.3, 156.4, 155.9, 149.7, 142.2, 137.9, 128.7, 124.5, 123.2, 122.1, 120.1, 117.2, 54.2, 47.5, 25.2, 23.8, 23.2, 22.5, 22.1. Anal. Calcd for $C_{24}H_{28}N_4S$: C, 71.25, H, 6.98, N, 13.85. Found: C, 71.27, H, 7.16, N, 13.72.

***N*-3-(*tert*-Butylsulfanyl)-4-[(1,3-dimethylbutyl)imino]-2,5-cyclohexadien-1-ylideneaniline (5.29h)**: Yield 97% (as a mixture of stereoisomers), orange oil; ^{1}H NMR δ 7.36-7.31 (m, 2H), 7.18 (d, *J* = 2.1 Hz, 1H), 7.12 (t, *J* = 7.5 Hz, 1H), 6.94 (dd, *J* = 10.5 Hz, *J* = 1.8 Hz, 1H),6.83–6.74 (m, 2H), 6.69 (s, 1H), 4.06–3.96 (m, 1H), 1.76–1.60 (m, 1H), 1.53 (d, *J* = 7.5 Hz, 9H), 1.49–1.15 (m, 5H), 0.96–0.82 (m, 6H); ^{13}C NMR δ 157.7, 156.6, 156.0, 150.0, 144.8, 140.3, 139.4, 137.7, 128.7, 125.2, 124.4, 124.3, 121.7, 121.0, 120.0, 54.3, 54.1, 47.4, 46.2, 46.0, 31.1, 31.0 30.8, 25.1, 25.0, 23.1, 22.6, 22.4 22.1. Anal. Calcd for $C_{22}H_{30}N_2S$: N, 7.90. Found: N, 8.05.

***N*-[4-[(1,3-Dimethylbutyl)imino]-3-(2-pyridinylsulfanyl)-2,5-cyclohexadien-1-ylidene]aniline (5.29i)**: Yield 55% (as a 1:1.4 ratio mixture of 1,4-benzenediamine and stereoisomers of 1,4-benzoquinone diimine), orange oil; ^{1}H NMR δ 8.69–8.63 (m, 2H), 7.76–7.52 (m, 4H), 7.38–7.10 (m, 8H), 7.08–6.93 (m, 2H), 6.87–6.76 (m, 4H), 3.98–3.92 (m, 1H), 3.72–3.65 (m, 1H), 1.57–1.00 (m, 14H), 0.90–0.60 (m, 12H); ^{13}C NMR δ 156.4, 156.0, 155.6, 154.7, 150.8, 150.6, 149.3, 149.2, 146.1, 142.0, 138.2, 137.4, 137.3, 137.1,

135.7, 133.2, 129.4, 129.0, 128.7, 128.3, 124.6, 124.3, 122.8, 122.6, 122.5, 121.4, 121.2, 120.7, 120.5, 120.2, 117.0, 54.1, 53.8, 47.3, 47.2, 24.9, 23.2, 23.1, 2.8, 22.6, 2.1, 21.9.. Anal. Calcd for $C_{23}H_{25}N_3S$: N, 11.19. Found: N, 11.22.

***N*-[4-Anilino-3-[(1,3-dimethylbutyl)imino]-6-(phenylimino)-1,4-cyclohexadien-1-yl]-*N*-phenylamine (5.31)**: *N*-(1,3-Dimethylbutyl)-N'-phenyl-*p*-quinone diimine (0.80 g, 3.0 mmol) was dissolved in toluene (15 mL) and treated with aniline (0.27 mL, 3.0 mmol) and *p*-toluenesulfonic acid (0.02 g). The dark purple reaction mixture was allowed to stirred for 20 h. Toluene was evaporated and the orange slurry was purified by a short silica gel column chromatography [Hex: EtOAc (9:1), and (1:1)] to give *N*-[4-anilino-3-[(1,3-dimethylbutyl)imino]-6-(phenylimino)-1,4-cyclohexadien-1-yl]-*N*-phenylamine (0.43 g, 64%) as red microcrystals and as a mixture of stereoisomers, mp 131–133 °C; ^{1}H NMR δ 8.29 (br s, 1H), 7.39–7.29 (m, 4H), 7.18 (pseudo t, *J* = 8.4 Hz, 2H), 7.11–7.02 (m, 4H), 6.98–6.94 (m, 3 H), 6.92–6.88 (m, 2H), 6.23 (d, *J* = 7.2 Hz, 1H), 6.16 (s, 1H), 5.36 (s, 1H), 3.25 (m, 1H), 1.63–1.54 (m, 1H), 1.49–1.40 (m, 1H), 1.24–1.12 (m, 1H), 1.10 (d, *J* = 6.3 Hz, 3H), 0.83 (d, *J* = 6.6 Hz, 3H), 0.74 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR δ 154.2, 150.6, 150.2, 146.0, 142.8, 139.6, 129.1, 128.9, 128.7, 124.0, 123.7, 123.4, 123.0, 121.0, 120.9, 120.7, 114.5, 113.8, 91.4, 87.5, 46.8, 45.7, 45.5, 25.0, 23.0, 22.5, 22.2, 20.2. Anal. Calcd for $C_{30}H_{32}N_4$: N, 12.46. Found: N, 12.06.

Diethyl 2-5-anilino-2-[(1,3-dimethylbutyl)amino]phenylmalonate (5.32a): To a solution of diethyl malonate (0.50 mL, 3.30 mmol) inside of an airless flask and dissolved in 15 mL of freshly distilled THF at -78 °C was added LDA dropwise and stirred for 15 minutes. *N*-(1,3-Dimethylbutyl)-N'-phenyl-p-quinone diimine (3.00 mmol)

(3.00 mmol) was added and the reaction mixture was stirred overnight from -78 °C to r.t. The reaction was quenched with 20 mL of NH4Cl, then extracted with 3x30 mL of CH2Cl2. The organic layer was dried (Na_2SO4), filtered (Celite), and the solvent was evaporated. Chromatography using Hex:EtOAc (9:1), (7:3) and (1:1) gave (diethyl 2-5-anilino-2-[(1,3-dimethylbutyl)amino]phenylmalonate (0.78 g, 61%) as yellow oil; ^{1}H NMR δ 7.15–7.06 (m, 3H), 6.65 (d, *J* = 7.8 HZ, 3H), 6.55–6.42 (m, 2H), 6.06 (s, 1H), 4.67 (s, 1H), 4.07–4.04 (m, 2H), 3.94–3.92 (m, 2H), 3.60–3.40 (m, 1H), 1.80–1.65 (m, 1H), 1.52–1.40 (m, 1H), 1.34–1.20 (m, 2H), 1.18–1.07 (m, 9H), 0.92 (pseudo t, J = 6.6 Hz, 6H); ^{13}C NMR δ 168.9, 146.3, 144.8, 130.9, 129.9, 128.7, 127.7, 117.8, 114.9, 113.8, 113.4, 61.6, 55.5, 46.7, 46.5, 24.9, 22.9, 2.4, 20.8, 13.8. Anal. Calcd for $C_{25}H_{34}N_2O_4$: N, 6.57. Found: N, 6.65.

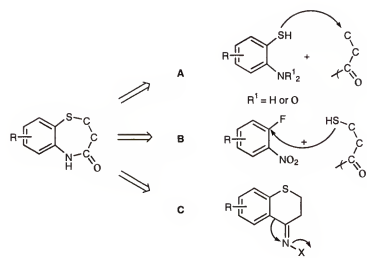
CHAPTER 6
NOVEL SYNTHESES OF 2,3-DIHYDRO-1,5-BENZOTHIAZEPIN-4(*5H*)-ONES AND 2H-1,4-BENZOTHIAZIN-3(*4H*)-ONES

6.1 Introduction

Over the past 20 years, syntheses of benzothiazepinones and benzothiazinones have been of great interest, due to their broad spectrum of biological activities. 1,5-Benzothiazepin-4-ones participate as calcium antagonists by interacting with the L-type voltage gated Ca^{2+} channel [93MI1, 85MI2]. Their uses for the treatment of cardiovascular disorders as vasodilators [73CPB92, 72MI3], as antiarythmic agents [73MI4], as spasmolytic [90CPB407], and angiotensive converting enzyme inhibitors [88MI5] and as antiulcer reagents [86CPB3844] have been well documented. Various benzothiazinones have been patented as therapeutic agents having antiinflamatory properties [76MI6] and as insecticides [79MI7]

The importance and utility of benzothiazepinones and benzothiazinones has led to the development of numerous synthetic routes [00JHC199, 79MI17]. For benzothiazepin-ones, the major approaches are cyclization and ring expansion. Depending on the retrosynthetic disconnection of the basic skeleton, these approaches can be subdivided into three different categories: A, B, and C [99JOC2219] (Scheme 6.1). In the approach A, nucleophilic attack of substituted 2-aminothiophenols or 2-nitrothiophenols on

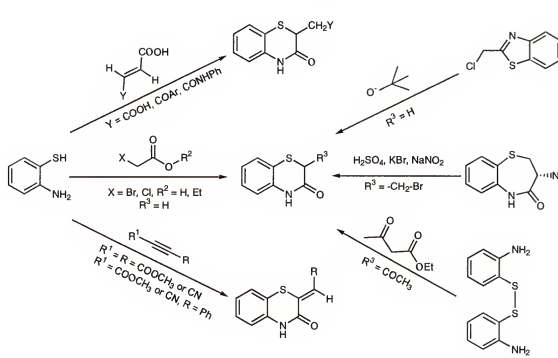
aliphatic electrophiles, such as β-halo-propionic acids [90JOC5572], α,β-unsaturated carboxylic acids [86T2731], β-propionolactones [87S724], malonic acids, or arylglycidic esters [92JOC851, 92JHC1605], afforded the desired products. In the approach B, 2-fluoronitroarenes were treated with a β-mercapto acid, followed by nitro group reduction and cyclization [85JMC1517]. A solid phase synthesis using approach B has been reported [99JOC2219]. In the approach C, ring expansion *via* Beckmann or Schmidt rearrangements of thiochromanone or thioflavone precursors produced the desired 6,7-fused ring systems [95SC1495, 76JCSP(1)2343] (Scheme 6.1).



Scheme 6.1

In the case of the benzothiazinones, similar nucleophilic reactions of 2-aminothiophenols have been employed. Benzothiazinones can be prepared i) by condensation of 2-aminobenzenethiol with β-benzoylacrylic acids, maleamic acids [59JACS1721], maleanilic/fumaranilic acids or esters [86T2731], acetylenic nitriles or esters [80JHC793], ii) by treatment of *N*-unsubstituted and *N,N'*-dialkyldithiodianilines

with β-ketoesters [92JHC11155], and iii) by reaction of 2-aminobenzenethiol with α-halogenacetic acids or esters [1897CB608, 1897CB2393]. Ring enlargement of 2-chloromethylbenzothiazole [97T5839] and ring contraction of benzothiazepinones [92LAC403] have also been reported to produce benzothiazinones (Scheme 6.2).



Scheme 6.2

During our investigation on the synthesis of 2-alkylthio-1,4-benzoquinone diimines [00JRC02], we determined that the nucleophilic addition of methyl 3-mercaptopropanoate ester to *N*-{4-[(1,3-dimethylbutyl)imino]-2,5-cyclohexadien-1-ylidene}aniline (**6.1a**) proceeded regioselectively by addition at the C-*3* position of the benzoquinoid ring forming methyl 3-(5-anilino-2-[(1,3-dimethylbutyl)amino]phenylsulfanyl)propanoate (**6.4a**). The structure of adduct **6.4a** was established [00JRC02] on the basis of NOE and 2D NMR experiments. In the present work, we have investigated

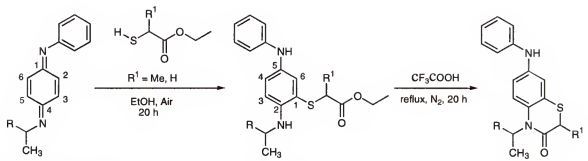
the syntheses of benzothiazepinones and benzothiazinones *via* additions of α- or β-mercaptoalkanoate esters and acids to benzoquinone diimines followed by cyclization.

6.2 Results and Discussion

2*H*-1,4-Benzothiazin-3(4*H*)-ones (6.3a-f). N^1-(Alkyl)-2-(alkylsulfanyl)-N^4-phenyl-1,4-benzenediamines **6.2a-f** were prepared in 87-97% yields by treatment of an *N*-4-[(alkyl)imino]-2,5-cyclohexadien-1-ylideneaniline (**6.1a-c**) with the corresponding α-mercaptoalkanoate ester. The ^{1}H NMR spectra of **6.2a-f** displayed a consistent chemical shift pattern containing a doublet (mixed with a triplet from the anilino group signals) at 7.12-7.21 ppm, a doublet at 6.70-6.72 ppm and a doublet of doublets at 6.47-6.50 ppm for the principal phenyl ring core with a sulfur atom at the C-3 position. These three signals could be assigned to protons attached to the C-3, C-6 and C-4 positions, respectively (see Scheme 6.3). The characteristic signals for the ethoxy group in the ^{1}H NMR spectra of compounds **6.2a-f** were a quartet at 3.96-4.24 ppm, and a triplet at 1.12-1.17 ppm, and the NH signal at the C-2 position appears as a broad singlet around 6.19-6.32 ppm. In the ^{13}C NMR spectra, the ethoxy group signals were found at 61.0-61.4 ppm and 13.8-14.0 ppm, and the ester carbonyl group signals were found at 170.0-173.0 ppm.

2*H*-1,4-Benzothiazin-3(4*H*)-ones **6.3a-f** were prepared in 89-97% yields by intramolecular cycloadditions of compounds **6.2a-f** on heating overnight with trifluoroacetic acid under reflux (Table 1). The structures **6.3a-f** were supported by CHN analytical data, high resolution mass spectroscopy, and ^{1}H and ^{13}C NMR spectra. Signals

corresponding to the ethoxy group found for compounds **6.2a-f** disappeared in the ^{1}H NMR and ^{13}C NMR spectra of compounds **6.3a-f**, suggesting that the cyclization took place. In ^{13}C NMR spectra, the signal of the newly formed quaternary lactam carbonyl in compounds **6.3a-f** is shifted upfield (about 6 ppm) to around 164.0-167.0 ppm.



6.1a, R = 2-methylpropyl
6.1b, R = 2-sectyl
6.1c, R = methyl

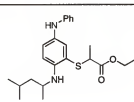
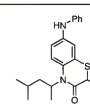
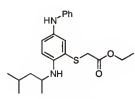
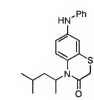
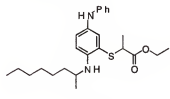
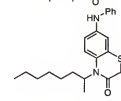
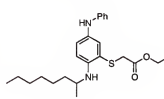
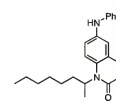
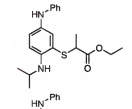
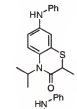
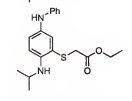
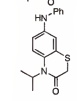
6.2a-f
(See Table 6.1)

6.2a-f
(See Table 6.1)

Scheme 6.3

Table 6.1

Preparation of N^1-(Alkyl)-2-(alkylsulfanyl)-N^4-phenyl-1,4-benzenediamines (**6.2a-f**) and 2*H*-1,4-Benzothiazin-3(*4H*)-ones (**6.3a-f**)

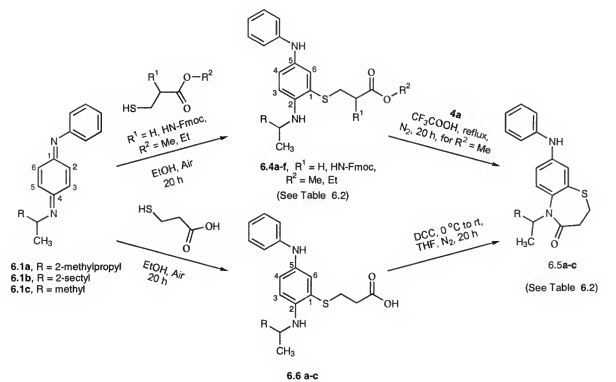
Entry	Product	Yield	Entry	Product	Yield
6.2a		90%	**6.3a**		91%
6.2b		87%	**6.3b**		97%
6.2c		97%	**6.3c**		93%
6.2d		95%	**6.3d**		90%
6.2e		89%	**6.3e**		93%
6.2f		94%	**6.3f**		89%

2,3-Dihydro-1,5-Benzothiazepin-4(*5H*)-ones (6.5a-c). Alkyl 3-{[5-anilino-2-(alkylami-no)phenyl]sulfanyl}propanoates **6.4a-f** were prepared in 86-92% yields by treatment of an *N*-4-[(alkyl)imino]-2,5-cyclohexadien-1-ylideneaniline (**6.1a-c**) with the corresponding β-mercaptoalkanoate ester (Scheme 6.4, Table 2). The assignment of protons at the C-3, C-6 and C-4 positions in the NMR spectra of compounds **6.4a-f** was comparable with that of compounds **6.2a-f**. In the case of compounds **6.4a-c**, the characteristic CH_2 peaks appeared at 2.94-2.97 ppm and 2.53-2.55 ppm and the methoxy group signal was found around 3.59-3.61 ppm.

Subsequently, cyclization of compounds **6.4a-f** by heating with trifluoroacetic acid at 70 °C was attempted. Benzothiazepinone **6.5a**, was thus obtained in 85% yield. The structure of benzothiazepinone **6.5a** was elucidated as follows. The ^{1}H NMR spectrum of the precursor **6.4a** showed a singlet at 3.62 ppm, characteristic of the methoxy group, and a set of two triplets at 2.55 and 2.98 ppm. After cyclization with trifluoroacetic acid, the methoxy group signal disappeared and the two triplets became a set of two broad singlets at 3.40 and 2.73 ppm in the ^{1}H NMR spectra of **6.5a**. This broadening of the signals can be attributed to the restricted rotation of the CH_2 groups in the benzothiazepinone ring. The new lactam carbonyl group has a signal with a chemical shift at 171.9 ppm in the ^{13}C NMR spectrum of **6.5a**.

Compounds **6.4b-f** failed to provide the desired cyclised **6.5b-f** under the reaction conditions mentioned above. We then attempted another approach to the synthesis of benzothiazepinones by treating benzoquinone diimines **6.1a-c** with 3-mercaptopropionic acid. It was envisioned that once the addition products 3-{[5-anilino-2-(alkylamino)phenyl]sulfanyl}-propanoic acid **6.6a-c** were made, cyclization could be

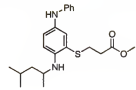
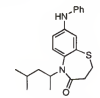
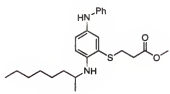
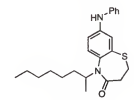
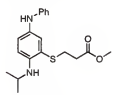
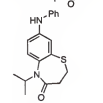
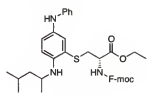
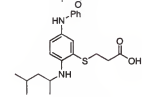
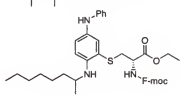
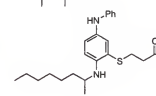
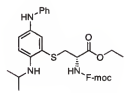
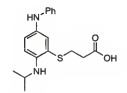
achieved upon addition of 1,3-dicyclohexylcarbodiimide (DCC) under Mitsunobu-type conditions (Scheme 6.4, Table 2). Intermediate compounds **6.6a-c** were isolated (but characterized only by ^{1}H NMR) and further used in the final cyclization step to obtain **6.5a-c**. The ^{13}C NMR spectra of **6.6a,b** were difficult to interpret due to the broadening of the peaks in the aromatic region. In the ^{1}H NMR spectra of **6.6a-c**, the peaks for the CH_2 groups appeared as a set of two triplets at 2.92-2.99 and 2.52-2.57 ppm respectively, and in the ^{13}C NMR spectra, the signals corresponding to the carboxylic acid moiety were found at 176.9-177.5 ppm.


6.1a, R = 2-methylpropyl
6.1b, R = 2-sectyl
6.1c, R = methyl
R1 = H, HN-Fmoc, R2 = Me, Et
EtOH, Air 20 h
6.4a-f, R1 = H, HN-Fmoc, R2 = Me, Et
(See Table 6.2)
4a
CF3COOH, reflux, N2, 20 h, for R2 = Me
6.5a-c
(See Table 6.2)
EtOH, Air 20 h
DCC, 0 °C to rt, THF, N2, 20 h
6.6 a-c

Scheme 6.4

Table 6.2

Preparation of Alkyl 3-{[5-anilino-2-(alkylamino)phenyl]sulfanyl}propanoates (**6.4a-f**), 3-{[5-anilino-2-(alkylamino)phenyl]sulfanyl}propanoic acid **6.6a-c** and 2,3-Dihydro-1,5-Benzothiazepin-4(*5H*)-ones (**6.5a-c**)

Entry	Product	Yield	Entry	Product	Yield
6.4a		90%	**6.5a**		85%
6.4b		89%	**6.5b**		97%
6.4c		86%	**6.5c**		81%
6.4d		88%	**6.6a**		71%
6.4e		90%	**6.6b**		63%
6.4f		92%	**6.6c**		70%

Treatment of the intermediates **6.6a-c** with DCC, and subsequent purification by flash column chromatography gave the compounds **6.5a-c** in 81-97% yields. Compounds **6.5a,b** were obtained as mixtures of conformers: ^{1}H NMR showed sets of two multiplets in a 1:1 ratio at 4.78-4.84 and at 4.68-4.75 ppm for **6.5a**, and at 4.68-4.75 and 4.50-4.57 ppm for **6.5b**. These signals were assigned to the CH proton adjacent to the alkyl amido group (proton 1'-H, Figure 6.1). The ^{13}C NMR spectra also displayed two peaks per carbon in both the aromatic and the alkyl region and the signal of the new lactam carbonyl group was found at 172.1 ppm for both **6.5a** and **6.5b**.

To justify our conclusions that the 7-membered rings display two different conformations at room temperature, a variable high temperature ^{1}H NMR experiment was performed. At 75 ºC, coalescence began to take effect, showing two broad singlets with chemical shifts at 4.69 and 4.76 ppm for **6.5a** and at 4.50 and 4.70 ppm for **6.5b**. By 90 ºC, a narrower peak was observed at 4.73 ppm for **6.5a** and a doublet with a chemical shift at 4.59 ppm was observed for **6.5b**. After 100 ºC, coalescence is at full, and a sharp singlet was observed at 4.71 and 4.62 ppm for compounds **6.5a** and **6.5b** accordingly. Significantly, the signals assigned to the methyl groups attached in the *N*-alkyl chain also showed some changes with temperature, being a complex set of doublets at room temperature but becoming a set of broad singlets at 100 ºC. It is believed that rapid ring inversion with no significant rotation around the CO-N bond would bring about the observed averaging of the signals [88JCSP(1)3399]. Since there are no substituents at the α-position of the lactam carbonyl group in compounds **6.5a,b**, a ring inversion would convert them into their mirror images [85LAC869] (Figure 6.1). The collected data for the variable temperature ^{1}H NMR has been summarized in Table 6.3.

This conformational phenomenon can be compared with those demonstrated by literature data on some benzothiazepinone derivatives [85LAC869], and also on similar 7-membered ring analogs [88JCSP(1)3399], [73T147]. Spectroscopic investigations using ^{1}H and ^{13}C NMR selective decoupling and two-dimensional NMR techniques have been employed for the structure elucidation of benzothiazepinone derivatives [85LAC869]. Ring inversion was observed and a dominant conformer in the equilibrium could be determined by analysis of the coupling constants [85LAC869].

For the case of similar 7-membered ring analogs, a systematic study by ^{1}H NMR of the effects of methyl- and phenyl-substitution in the heterocyclic rings of a series of 1,5-benzodiazepines and some analogous 1,5-benzothiazepines has been reported using variable temperature measurements [73T147]. In several cases, a change in ring conformation at room temperature was observed. Also, variable temperature ^{1}H NMR spectroscopy of 1-substituted 1,3,4,5-tetrahydro-2*H*-1-benzazepin-2-ones has been reported [88JCSP(1)3399]. The barrier to ring inversion from the observed coalescence temperature was calculated and a boat ↔ boat inversion conformation *via* rapid ring inversion with no significant rotation about the CO-N bond has been proposed.

Figure 6.1

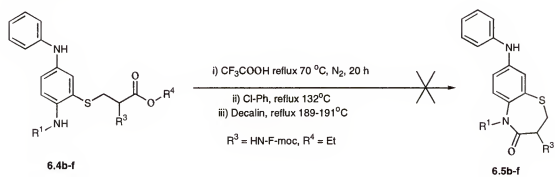
Table 6.3

Variable Temperature 300MHz ^{1}H NMR Spectroscopy of 2,3-Dihydro-1,5-Benzothiazepin-4(*5H*)-ones **6.5a** and **6.5b**

	6.5a			**6.5b**		
Temp (°C)	1'-H (ppm)	2-H (ppm)	3-H (ppm)	1'-H (ppm)	2-H (ppm)	3-H (ppm)
25	m (4.78-4.84) m (4.68-4.75)	m (3.20-3.28)	m (2.41-2.51)	m (4.72-4.79) m (4.53-4.59)	m (3.24-3.27)	m (2.41-2.52)
50	m (4.78-4.85) m (4.68-4.75)	m (3.22-3.28)	m (2.40-2.50)	m (4.68-4.75) m (4.50-4.57)	m (3.26-3.29)	m (2.44-2.50)
75	br s (4.76) br s (4.69)	br s (3.50)	br s (2.47)	br s (4.70) br s (4.50)	br s (3.26)	br s (2.48)
90	d (4.73)	br s (3.25)	br s (2.46)	d (4.59)	br s (3.26)	br s (2.47)
100	br s (4.71)	br s (3.25)	br s (2.46)	br s (4.62)	br s (3.25)	br s (2.47)

6.2.1 Unsuccessful attempts

Compounds **6.4b-f** failed to provide the desired adducts **6.5b-f** by heating with trifluoroacetic acid at 70 °. Refluxing compounds **6.4d-f** in chlorobenzene for two days led only to recovery of the starting materials. When decalin was used as a solvent, decomposition of the starting materials occurred after heating at 190 °C for three days (Scheme 6.5).



Scheme 6.5

In summary, we have developed a new method to produce benzothiazepinones and benzothiazinones. This clean and efficient two-step synthesis for these target compounds provides a novel synthetic tool for their preparation. Employing an *N*-phenyl group at the C-1 position as an electron acceptor group to accommodate for the addition of an α- or β-mercaptoalkanoate ester or acid nucleophile at the C-3 position of the benzoquinone diimine enables to control the regioselectivity of the nucleophilic attack resulting in only one regioisomer.

6.3 Experimental Section

General Methods. Absolute ethanol 200 proof was used as a solvent for the addition of thiol esters and acids to benzoquinone diimines. Starting material **6.6.1a** is commercially available from Flexsys America L. P., whereas **6.6.1b,c** were obtained upon oxidation of the corresponding commercially available benzenediamines with Ag_2O [00JRC02]. Trifluoroacetic acid was obtained from Fischer or Aldrich. All cyclization reactions were carried out under nitrogen atmosphere. Column chromatography was conducted with silica gel 230-400 mesh. All NMR spectra were recorded in $CDCl_3$ using a Varian VXR 300 NMR Spectrometer. Melting points were measured using a Mel-Temp apparatus.

General Procedure for the Preparation of *N*-4-[(Alkyl)imino]-2,5-cyclohexadien-1-ylideneanilines 6.6.1b-c. The corresponding 1,4-benzenediamine (10.0 mmol) was dissolved in toluene (25 mL) and treated with Ag_2O (4.63 g, 20.0 mmol) and $MgSO_4$ (3.37 g, 28.0 mmol) for 20 h. The orange slurry was filtered (Celite), evaporated and purified by flash silica gel column chromatography [Hex: EtOAc (9:1) and (1:1)] to give the corresponding *N*-4-[(alkyl)imino]-2,5-cyclohexadien-1-ylideneaniline as a mixture of stereoisomers.

***N*-[4-(Phenylimino)-2,5-cyclohexadien-1-ylidene]-2-octanamine (6.6.1b).** Yield 99% (as a 6:4 ratio mixture of stereoisomers), orange oil, ^{1}H NMR δ (major isomer): 7.37 (d, J = 7.6 Hz, 2H), 7.15 (t, J = 7.0 Hz, 1H), 6.99–6.92 (m, 2H), 6.88–6.80 (m, 2H), 6.77–6.71 (m, 2H), 3.96–3.83 (m, 1H), 1.66–1.61 (m, 2H), 1.27–1.19 (m, 11H), 0.87–0.85 (m, 3H); ^{13}C NMR δ (major isomer): 158.7, 157.2, 150.1, 139.1, 136.8, 128.9, 124.7, 120.4, 56.3,

38.4, 31.7, 29.2, 26.6, 22.6, 22.3, 14.0. ^{13}C NMR δ (minor isomer): 158.7, 157.0, 150.1, 137.9, 134.3, 124.7, 122.3, 121.8, 56.4, 38.4, 31.7, 29.2, 26.6, 22.4, 22.3, 14.0. Anal. Calcd for $C_{20}H_{26}N_2$: N, 9.51. Found: N, 9.59.

***N*-[4-(Isopropylimino)-2,5-cyclohexadien-1-ylidene]aniline (6.6.1c).** Yield 99% (as a 6:4 ratio mixture of stereoisomers), orange oil, ^{1}H NMR δ 7.37 (t, *J* = 7.2 Hz, 2H), 7.15 (t, *J* = 6.3 Hz, 2H), 7.00–6.91 (m, 2H), 6.86 (d, *J* = 7.2 Hz, 2H), 6.79–6.72 (m, 1H), 4.16–4.02 (m, 1H), 1.28–1.24 (m, 6H); ^{13}C NMR δ (major isomer): 158.6, 156.8, 150.1, 139.0, 136.9, 128.8, 124.7, 122.9, 121.7, 120.3, 51.5, 24.0. ^{13}C NMR δ (minor isomer): 158.4, 156.7, 150.0, 137.8, 134.4, 124.7, 122.1, 120.4, 51.6, 24.1.Anal. Calcd for $C_{15}H_{16}N_2$: N, 12.49. Found: N, 12.65.

General Procedure for the Preparation of N^1-(Alkyl)-2-(alkylsulfanyl)-N^4-phenyl-1,4-benzenediamines 6.2a-f and Alkyl 3-{[5-anilino-2-(alkylamino)phenyl]sulfanyl}-propanoates 6.4a-f. The corresponding benzoquinone diimine (3.0 mmol) was dissolved in ethanol (25 mL) and treated with a mercaptoester derivative (3.0 mmol) under a constant gentle stream of air. The dark reaction mixture was stirred for 20 h. The solvent was evaporated and the dark brown slurry was purified by silica gel column chromatography [Hex: EtOAc (9:1), (7:3) and (1:1)] to give the corresponding 2-alkylthio-1,4-benzenediamines.

Ethyl 2-(5-anilino-2-[(1,3-dimethylbutyl)amino]phenylsulfanyl)propanoate (6.2a). Yield 90% (as a 2.2:1 ratio mixture of isomers), orange oil; ^{1}H NMR δ (major isomer): 7.23–7.15 (m, 3H), 7.00–6.96 (m, 2H), 6.86–6.75 (m, 2H), 6.56–6.52 (m, 1H), 6.29 (s, 1H), 4.01 (q, *J* = 14.4, 7.2 Hz, 2H), 3.68–3.59 (m, 1H), 3.57–3.44 (m, 1H), 3.21 (br s,

1H), 1.77–1.73 (m, 1H), 1.50–1.43 (m, 3H), 1.32–1.23 (m, 2H), 1.17–1.11 (m, 3H), 0.93 (t, J = 7.2 Hz, 6H); ^{1}H NMR (minor isomer): 7.23–7.15 (m, 3H), 7.00–6.96 (m, 2H), 6.86–6.75 (m, 2H), 6.56–6.52 (m, 1H), 6.29 (s, 1H), 4.20 (q, J = 14.4, 7.2 Hz, 2H), 3.68–3.59 (m, 1H), 3.57–3.44 (m, 1H), 3.21 (br s, 1H), 1.77–1.73 (m, 1H), 1.50–1.43 (m, 3H), 1.32–1.23 (m, 2H), 1.17–1.11 (m, 3H), 0.93 (t, J = 7.2 Hz, 6H). ^{13}C NMR δ (major isomer): 172.8, 144.6, 142.6, 129.2, 129.1, 124.0, 119.8, 116.4, 115.7, 114.6, 113.9, 61.2, 47.1, 46.8, 45.2, 25.0, 22.9, 22.5, 21.0, 17.4, 13.9. ^{13}C NMR δ (minor isomer): 172.8, 146.3, 140.0, 135.1, 129.1, 123.2, 120.5, 118.5, 115.7, 114.6, 113.4, 61.4, 47.9, 46.8, 45.1, 25.0, 22.9, 22.8, 21.0, 16.7, 14.1. Anal. Calcd for $C_{23}H_{32}N_2O_2S$: N, 6.99. Found: N, 7.34.

Ethyl 2-(5-anilino-2-[(1,3-dimethylbutyl)amino]phenylsulfanyl)acetate (6.2b). Yield 87%, orange oil; ^{1}H NMR δ 7.24–7.14 (m, 3H), 6.92 (d, J = 7.8 Hz, 2H), 6.81 (t, J = 7.2 Hz, 1H), 6.77 (d, J = 2.6 Hz, 1H), 6.51(dd, J = 8.7, 2.6 Hz, 1H), 6.19 (s, 1H), 4.06 (q, J = 14.1, 7.2 Hz, 2H), 3.52–3.41 (m, 3H), 3.23 (br s, 1H), 1.80–1.69 (m, 1H), 1.52–1.41 (m, 1H), 1.35–1.22 (m, 1H), 1.20–1.14 (m, 6H), 0.93 (t, J = 6.8 Hz, 6H); ^{13}C NMR δ 170.0, 145.0, 143.4, 133.6, 129.2, 126.2, 122.0, 119.5, 118.2, 115.9, 114.7, 61.5, 47.0, 46.9, 37.3, 25.0, 22.9, 22.6, 21.0, 14.0. Anal. Calcd for $C_{22}H_{30}N_2O_2S$: N, 7.25. Found: N, 7.37.

Ethyl 2-(5-anilino-2-[(1-methylheptyl)amino]phenylsulfanyl)propanoate (6.2c). Yield 97% (as a 4:1 ratio mixture of isomers), orange oil; ^{1}H NMR δ (major isomer): 7.22–7.15 (m, 3H), 6.96 (d, J = 7.8 Hz, 2H), 6.82 (t, J = 7.5 Hz, 1H), 6.79 (brs, 1H), 6.53 (dd, J = 8.7, 2.4 Hz, 1H), 6.30 (s, 1H), 4.00 (q, J =14.1, 6.9 Hz, 2H), 3.66 (q, J = 14.1, 7.2 Hz, 1H), 3.38–3.34 (m, 1H), 3.23 (br s, 1H), 1.53–1.20 (m, 13H), 1.16–1.10 (m, 6H), 0.88 (t,

J = 6.0 Hz, 3H); ^{1}H NMR δ (minor isomer): 7.22–7.15 (m, 3H), 6.96 (d, J = 7.8 Hz, 2H), 6.82 (t, J = 7.5 Hz, 1H), 6.79 (brs, 1H), 6.53 (dd, J = 8.7, 2.4 Hz, 1H), 6.30 (s, 1H), 4.19 (q, J = 14.1, 7.2 Hz, 2H), 3.59-3.56 (m, 1H), 3.38–3.34 (m, 1H), 3.23 (br s, 1H), 1.53–1.20 (m, 13H), 1.16–1.10 (m, 6H), 0.88 (t, J = 6.0 Hz, 3H); ^{13}C NMR δ (major isomer): 172.7, 144.6, 142.6, 135.0, 129.1, 123.1, 120.6, 119.7, 116.3, 115.7, 61.3, 61.1, 49.1, 45.1, 37.1, 31.7, 31.5, 29.3, 26.0, 22.5, 20.7, 17.3, 14.0. ^{13}C NMR δ (minor isomer): 172.7, 144.6, 142.6, 135.0, 129.1, 123.1, 120.6, 119.7, 116.3, 115.7, 61.3, 61.1, 49.0, 45.0, 37.1, 31.7, 31.5, 29.3, 26.0, 22.5, 20.6, 17.3, 14.0. Anal. Calcd for $C_{25}H_{36}N_2O_2S$: N, 6.54. Found: N, 6.54.

Ethyl 2-(5-anilino-2-[(1-methylheptyl)amino]phenylsulfanyl)acetate (6.2d). Yield 95%, orange oil; ^{1}H NMR δ 7.21–7.12 (m, 3H), 6.90 (d, J = 7.8 Hz, 2H), 6.81 (t, J = 7.2 Hz, 1H), 6.76 (d, J = 2.7 Hz, 1H), 6.49 (dd, J = 8.7, 2.7 Hz, 1H), 6.19 (s, 1H), 4.05 (q, J = 14.4, 7.2 Hz, 2H), 3.47 (s, 2H), 3.40–3.35 (m, 1H), 3.27 (br s, 1H), 1.53–1.46 (m, 1H), 1.37–1.20 (m, 9H), 1.16 (t, J = 6.6 Hz, 6H), 0.88 (t, J = 6.6 Hz, 3H); ^{13}C NMR δ 170.0, 145.0, 143.4, 13.5, 129.1, 126.2, 123.9, 121.9, 119.4, 118.0, 115.8, 114.6, 113.9, 61.3, 48.9, 37.1, 31.7, 29.3, 26.0, 22.5, 20.6, 14.0. Anal. Calcd for $C_{24}H_{34}N_2O_2S$: N, 6.76. Found: N, 6.78.

Methyl 2-{[5-anilino-2-(isopropylamino)phenyl]sulfanyl}propanoate (6.2e). Yield 89%, orange oil; ^{1}H NMR δ 7.22–7.12 (m, 3H), 6.96 (d, J = 7.8 Hz, 2H), 6.82 (t, J = 7.5 Hz, 1H), 6.80 (s, 1H), 6.53 (d, J = 8.6 Hz, 1H), 6.32 (s, 1H), 3.99 (q, J = 14, 7.2 Hz, 2H), 3.66 (q, J = 7.2 Hz, 1H), 3.58–3.50 (m, 1H), 3.21 (br s, 1H), 1.42 (d, J = 7.2 Hz, 3H), 1.18 (d, J = 5.9 Hz, 6H), 1.12 (t, J = 7.2 Hz, 3H); ^{13}C NMR δ 172.7, 144.4, 142.3, 135.1,

129.0, 122.9, 120.6, 120.2, 119.7, 116.3, 115.9, 61.0, 45.0, 44.6, 22.8, 17.2, 13.8. Anal. Calcd for $C_{20}H_{26}N_2O_2S$: N, 7.81. Found: N, 8.02.

Methyl 2-{[5-anilino-2-(isopropylamino)phenyl]sulfanyl}acetate (6.2f). Yield 94%, yellow microcrystals mp 47–50 °C; ^{1}H NMR δ 7.21–7.13 (m, 3H), 6.91 (d, *J* = 7.8 Hz, 2H), 6.80 (t, *J* = 7.3 Hz, 1H), 6.78 (d, *J* = 2.3 Hz, 1H), 6.50 (dd, *J* = 8.7, 2.6 Hz, 1H), 6.20 (s, 1H), 4.05 (q, *J* = 7.2 Hz, 2H), 3.57–3.53 (m, 1H), 3.47 (s, 2H), 3.18 (br s, 1H), 1.19 (d, *J* = 6.2 Hz, 6H), 1.16 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR δ 170.0, 144.9, 143.1, 133.7, 129.1, 126.1, 121.8, 119.4, 118.2, 115.9, 114.9, 61.4, 44.6, 37.2, 22.9, 13.9. Anal. Calcd for $C_{19}H_{24}N_2O_2S$: C, 66.25; H, 7.02; N, 8.13. Found: C, 66.18; H, 7.31; N, 8.11.

Methyl 3-(5-anilino-2-[(1,3-dimethylbutyl)amino]phenylsulfanyl)propanoate (6.4a). Yield 90%, yellow oil [00JRC02].

Methyl 3-({5-anilino-2-[(1-methylheptyl)amino]phenyl}sulfanyl)propanoate (6.4b). Yield 89%, orange oil; ^{1}H NMR δ 7.21–7.13 (m, 3H), 6.91 (d, *J* = 7.8, 2H), 6.80 (t, *J* = 7.2 Hz, 1H), 6.70 (d, *J* = 2.7 Hz, 1H), 6.48 (dd, *J* = 8.7, 2.7 Hz, 1H), 6.06 (s, 1H), 3.61 (s, 3H), 3.41–3.35 (m, 1H), 3.28 (br s, 1H), 2.94 (t, *J* = 7.2 Hz, 2H), 2.55 (t, *J* = 6.9 Hz, 2H), 1.55–1.49 (m, 1H), 1.44–1.20 (m, 9H), 1.16 (d, *J* = 6.3 Hz, 3H), 0.88 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR δ 172.1, 145.0, 143.2, 133.6, 129.1, 125.8, 121.5, 119.5, 118.2, 115.9, 114.2, 51.7, 48.9, 37.1, 33.9, 31.7, 29.4, 29.3, 26.0, 22.5, 20.7, 14.0. Anal. Calcd for $C_{24}H_{34}N_2O_2S$: C, 69.53; H, 8.27;N, 6.76. Found: C, 69.81; H, 8.40; N, 7.08.

Methyl 3-{[5-anilino-2-(isopropylamino)phenyl]sulfanyl}propanoate (6.4c). Yield 86%, orange oil; ^{1}H NMR δ 7.21–7.13 (m, 3H), 6.91 (d, *J* = 7.6 Hz, 2H), 6.81 (t, *J* = 7.3

Hz, 1H), 6.72 (d, *J* = 2.7 Hz, 1H), 6.50 (dd, *J* = 8.6, 2.6 Hz, 1H), 6.08 (s, 1H), 3.61 (s, 3H), 3.58–3.54 (m, 1H), 3.22 (br s, 1H), 2.97 (t, *J* = 7.2 Hz, 2H), 2.55 (t, *J* = 7.2 Hz, 2H), 1.19 (d, *J* = 6.2 Hz, 6H); ^{13}C NMR δ 172.1, 144.9, 142.9, 133.7, 129.1, 125.6, 121.4, 119.5, 118.3, 115.9, 114.4, 51.6, 44.6, 33.9, 29.3, 22.8. Anal. Calcd for $C_{19}H_{24}N_2O_2S$: N, 8.13. Found: N, 8.04.

Ethyl (2*R*)-3-({5-anilino-2-[(1,3-dimethylbutyl)amino]phenyl}sulfanyl)-2-{[(9*H*-fluoren-9-ylmethoxy)carbonyl]amino}propanoate (6.4d). Yield 88% (as a mixture of stereoisomers), orange oil; ^{1}H NMR δ 7.74 (d, *J* = 7.3 Hz, 2H), 7.56 (d, *J* = 7.3 Hz, 2H), 7.39 (t, *J* = 7.3 Hz, 2H), 7.28 (t, *J* = 7.3 Hz, 2H), 7.19 (t, *J* = 7.6 Hz, 2H), 7.12 (d, *J* = 8.5 Hz, 2H), 6.94 (d, *J* = 7.9 Hz, 2H), 6.82 (t, *J* = 7.3 Hz, 1H), 6.75 (s, 1H), 6.46 (d, *J* = 8.5 Hz, 1H), 6.04 (s, 1H), 5.73 (d, *J* = 8.2 Hz, 1H), 4.60–4.56 (m, 1H), 4.37–4.20 (m, 2H), 4.17–4.06 (m, 2H), 4.03–3.97 (m, 1H), 3.44–3.40 (m, 1H), 3.35–3.18 (m, 2H), 1.73–1.69 (m, 1H), 1.46–1.32 (m, 1H), 1.29–1.10 (m, 7H), 0.90 (t, *J* = 6.7 Hz, 6H); ^{13}C NMR δ 170.4, 155.5, 144.8, 143.7, 143.3, 141.1, 133.9, 129.2, 128.8, 127.6, 127.0, 125.1, 121.6, 120.3, 119.8, 119.7, 118.8, 116.2, 114.5, 67.1, 61.8, 54.0, 47.0, 46.7, 37.4, 31.5, 25.0, 22.9, 22.5, 21.0, 14.0. Anal. Calcd for $C_{38}H_{43}N_3O_4S$: N, 6.59. Found: N, 6.39.

Ethyl (2*R*)-3-({5-anilino-2-[(1-methylheptyl)amino]phenyl}sulfanyl)-2-{[(9*H*-fluoren-9-ylmethoxy)carbonyl]amino}propanoate (6.4e). Yield 90%, orange oil; ^{1}H NMR δ 7.71 (d, *J* = 7.3 Hz, 2H), 7.54 (d, *J* = 7.3 Hz, 2H), 7.35 (t, *J* = 7.3 Hz, 2H), 7.25 (t, *J* = 7.3 Hz, 2H), 7.18 (t, *J* = 7.9 Hz, 2H), 7.10 (d, *J* = 8.8 Hz, 2H), 6.92 (d, *J* = 7.9 Hz, 2H), 6.81 (t, *J* = 7.3 Hz, 1H), 6.75 (s, 1H), 6.43 (dd, *J* = 8.5, 2.3 Hz, 1H), 6.04 (s, 1H), 5.77 (d, *J* = 7.9 Hz, 1H), 4.57–4.53 (m, 1H), 4.36–4.21 (m, 2H), 4.18–4.08 (m, 2H), 4.06–3.93 (m,

1H), 3.32–3.00 (m, 4H), 1.51–1.48 (m, 1H), 1.31–1.16 (m, 1H), 1.14–1.08 (m, 6H), 0.88–0.84 (m, 3H); ^{13}C NMR δ 170.3, 155.4, 144.8, 143.6, 143.3, 141.0, 133.7, 129.5, 129.1, 126.9, 125.4, 125.0, 121.6, 119.7, 119.6, 118.7, 116.1, 114.4, 67.0, 61.6, 53.9, 48.7, 46.9, 37.2, 37.0, 31.7, 29.2, 26.0, 22.5, 20.5, 14.0, 13.9. Anal. Calcd for $C_{40}H_{47}N_3O_4S$: C, 72.14; H, 7.13; N, 6.31. Found: C, 72.26; H, 7.36; N, 6.32.

Ethyl (2*R*)-3-{[5-anilino-2-(isopropylamino)phenyl]sulfanyl}-2-{[(9*H*-fluoren-9-ylmethoxy)carbonyl]amino}propanoate (6.4f). Yield 92%, beige microcrystals mp 58–61 °C; ^{1}H NMR δ 7.75 (d, *J* = 7.3 Hz, 2H), 7.56 (d, *J* = 7.3 Hz, 2H), 7.38 (t, *J* = 7.3 Hz, 2H), 7.28 (t, *J* = 7.3 Hz, 2H), 7.20 (t, *J* = 7.9 Hz, 2H), 7.12 (d, *J* = 8.8 Hz, 2H), 6.94 (d, *J* = 7.9 Hz, 2H), 6.83 (t, *J* = 7.3 Hz, 1H), 6.78 (s, 1H), 6.47 (dd, *J* = 8.8, 2.0 Hz, 1H), 6.06 (s, 1H), 5.71 (d, *J* = 7.9 Hz, 1H), 4.58–4.56 (m, 1H), 4.36–4.25 (m, 2H), 4.20–4.10 (m, 2H), 4.07–3.98 (m, 1H), 3.55–3.49 (m, 1H), 3.35–3.17 (m, 2H), 1.20–0.88 (m, 9H); ^{13}C NMR δ 170.4, 155.5, 144.8, 143.8, 143.0, 141.2, 134.3, 129.2, 127.6, 127.0, 125.1, 125.0, 121.5, 119.9, 119.8, 119.1, 116.5, 115.0, 67.2, 61.8, 54.1, 47.1, 44.7, 37.4, 23.0, 14.0. Anal. Calcd for $C_{35}H_{37}N_3O_4S$: C, 70.56; H, 6.26; N, 7.05. Found: C, 70.63; H, 6.70; N, 6.90.

General Procedure for the Preparation of 3-{[5-anilino-2-(alkylamino)phenyl]-sulfanyl}propanoic acids 6a-c. The corresponding benzoquinone diimine (3.0 mmol) was dissolved in ethanol (25 mL) and treated with 3-mercaptopropionic acid (0.33 mL, 3.0 mmol) under a constant gentle stream of air. The dark reaction mixture was allowed to stir for 20 h. The solvent was evaporated and the dark brown slurry was purified by

silica gel column chromatography [Hex: EtOAc (9:1), (7:3) and (1:1)] to give the corresponding 3-{[5-anilino-2-(alkylamino)phenyl]sulfanyl}propanoic acid.

3-{(5-Anilino-2-[(1,3-dimethylbutyl)amino]phenylsulfanyl)}propanoic acid (6.6a). Yield 71%, brown oil, used without further purification. ^{1}H NMR δ 7.42–6.29 (m, 10H), 3.48 (br s, 1H), 2.88 (t, *J* = 7.0 Hz, 2H), 2.52 (t, *J* = 7.0 Hz, 2H), 1.86–1.65 (m, 1H), 1.62–1.46 (m, 1H), 1.34–1.19 (m, 2H), 1.15 (d, *J* = 6.1 Hz, 3H), 0.96–0.80 (m, 6H).

3-{(5-Anilino-2-[(1-methylheptyl)amino]phenylsulfanyl)}propanoic acid (6.6b). Yield 63%, brown oil, used without further purification. ^{1}H NMR δ 7.89–6.40 (m, 10H), 3.45 (br s, 1H), 2.92 (t, *J* = 7.0 Hz, 2H), 2.57 (t, *J* = 7.0 Hz, 2H), 1.80–1.50 (m, 1H), 1.48–1.23 (m, 10H), 1.19 (d, *J* = 6.7 Hz, 3H), 0.88 (t, *J* = 5.8 Hz, 3H).

3-{[5-Anilino-2-(isopropylamino)phenyl]sulfanyl}propanoic acid (6.6c). Yield 70%, brown oil, used without further purification. ^{1}H NMR δ 7.96 (br s, 2H), 7.22–7.11 (m, 3H), 7.04–6.87 (m, 3H), 6.81 (d, *J* = 8.2 Hz, 1H), 6.77 (t, *J* = 7.0 Hz, 1H), 6.63 (d, *J* = 8.8 Hz, 1H), 3.61–3.53 (m, 1H), 2.92 (t, *J* = 7.0 Hz, 2H), 2.54 (t, *J* = 7.0 Hz, 2H), 1.22 (t, *J* = 6.4 Hz, 6H).

General Procedure for the Preparation of Benzothiazinones 6.3a-f (and Benzothiazepinone 6.5a). The corresponding 2-alkylthio-1,4-benzenediamine (3.4 mmol) was dissolved in trifluoroacetic acid (15 mL) and the dark reaction mixture was allowed to stir at 70 °C (reflux) for 20 h under nitrogen. Trifluoroacetic acid was evaporated CH_2Cl_2 (50 mL) was added to the dark slurry. The organic layer was washed with saturated sodium bicarbonate, and water, dried ($MgSO_4$), and filtered (Celite). The solvent was evaporated

and the dark slurry was purified by silica gel column chromatography [Hex: EtOAc (9:1), (7:3) and (1:1)] to give the desired benzothiazepinones or benzothiazinones.

7-Anilino-4-(1,3-dimethylbutyl)-2-methyl-2*H*-1,4-benzothiazin-3(4*H*)-one (6.3a). Yield 91% (as a 1:1 ratio mixture of diastereomers), brown microcrystals mp 49–52 °C; ^{1}H NMR δ 7.44 (t, *J* = 7.2 Hz, 2H), 7.34 (t, *J* = 7.3 Hz, 1H), 7.20 (d, *J* = 7.3 Hz, 2H), 6.54 (d, *J* = 2.3 Hz, 1H), 6.28 (d, *J* = 8.9 Hz, 1H), 6.23 (dd, *J* = 8.7, 2.3 Hz, 1H), 3.65 (q, *J* = 14.0, 7.0 Hz, 1H), 3.43 (q, *J* = 12.9, 6.4 Hz, 1H), 3.38 (br s, 1H), 1.77–1.68 (m, 1H), 1.54 (d, *J* = 7.0 Hz, 3H), 1.47–1.38 (m, 1H), 1.29–1.19 (m, 1H), 1.13 (d, *J* = 6.1 Hz, 3H), 0.91 (t, *J* = 7.6 Hz, 6H); ^{13}C NMR δ (major isomer): 167.1, 143.9, 140.2, 131.4, 129.5, 128.6, 127.6, 123.5, 121.1, 111.8, 111.4, 46.7, 46.6, 38.7, 25.0, 22.8, 22.5, 20.9, 14.9. ^{13}C NMR δ (minor isomer): 167.1, 143.9, 140.2, 131.4, 129.5, 128.6, 127.6, 123.4, 121.1, 111.8, 111.4, 46.8, 46.6, 38.7, 25.0, 22.8, 22.5, 20.9, 14.9. HRMS calcd for $C_{21}H_{26}N_2O_2S$ (M): 354.1766, found: 354.1784.

7-Anilino-4-(1,3-dimethylbutyl)-2*H*-1,4-benzothiazin-3(4*H*)-one (6.3b). Yield 97% (as a 1:1 ratio mixture of diastereomers), yellow oil; ^{1}H NMR δ 7.40 (t, *J* = 7.3 Hz, 2H), 7.31 (d, *J* = 7.3 Hz, 1H), 7.18 (d, *J* = 7.5 Hz, 2H), 6.51 (d, *J* = 2.5 Hz, 1H), 6.27 (d, *J* = 8.9 Hz, 1H), 6.19 (dd, *J* = 8.9, 2.5 Hz, 1H), 3.49–3.37 (m, 4H), 1.73–1.65 (m, 1H), 1.44–1.34 (m, 1H), 1.25–1.16 (m, 1H), 1.09 (d, *J* = 6.1 Hz, 3H), 0.88 (pseudo t, *J* = 6.7 Hz, 6H); ^{13}C NMR δ (major isomer) 164.2, 143.8, 139.6, 131.5, 129.3, 128.4, 127.5, 124.3, 121.3, 111.5, 111.0, 46.4, 32.2, 24.8, 22.7, 22.4, 22.4, 20.7. ^{13}C NMR δ (minor isomer) 164.2, 143.8, 139.6, 131.5, 129.3, 128.4, 127.5, 124.3, 121.3, 111.5, 111.0, 46.3, 32.2, 24.8,

22.7, 22.4, 22.4, 20.7. Anal. Calcd for $C_{20}H24N_2OS$: N, 8.23. Found: N, 8.15. HRMS calcd for $C_{20}H_{24}N_2OS$ (M): 340.1609, found: 340.1624.

7-Anilino-2-methyl-4-(1-methylheptyl)-2*H*-1,4-benzothiazin-3(4*H*)-one (6.3c). Yield 93% (as a 1:1 ratio mixture of diastereomers), yellow oil; ^{1}H NMR δ 7.42 (t, *J* = 7.3 Hz, 2H), 7.32 (t, *J* = 7.3 Hz, 1H), 7.19 (d, *J* = 7.5 Hz, 2H), 6.53 (d, *J* = 2.2 Hz, 1H), 6.28 (d, *J* = 8.9 Hz, 1H), 6.21 (dd, *J* = 8.9, 2.3 Hz, 1H), 3.64 (q, *J* = 14.0, 7.0 Hz, 1H), 3.44 (br s, 1H), 3.38–3.32 (m, 1H), 1.53 (d, *J* = 7.0 Hz, 3H), 1.50–1.47 (m, 1H), 1.43–1.27 (m, 9H), 1.13 (d, *J* = 6.1 Hz, 3H), 0.87 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR δ (major isomer) 167.0, 143.9, 140.1, 131.2, 129.4, 128.5, 127.5, 123.3, 120.9, 111.5, 111.3, 48.5, 38.5, 37.0, 31.7, 29.2, 25.9, 22.5, 20.6, 14.9, 14.0. ^{13}C NMR δ (minor isomer) 167.0, 143.9, 140.1, 131.2, 129.4, 128.5, 127.5, 123.3, 121.0, 111.8, 111.3, 48.5, 38.5, 37.0, 31.7, 29.2, 25.9, 22.5, 20.6, 14.9, 14.0. HRMS calcd for $C_{23}H_{30}N_2OS$ (M): 382.2079, found: 382.2113.

7-Anilino-4-(1-methylheptyl)-2*H*-1,4-benzothiazin-3(4*H*)-one (6.3d). Yield 90%, yellow oil; ^{1}H NMR δ 7.43 (t, *J* = 7.3 Hz, 2H), 7.33 (t, *J* = 7.3 Hz, 1H), 7.20 (d, *J* = 8.2 Hz, 2H), 6.53 (s, 1H), 6.30 (d, *J* = 8.8 Hz, 1H), 6.21 (d, *J* = 9.1 Hz, 1H), 3.51–3.46 (m, 3H), 3.35–3.33 (m, 1H), 1.49–1.47 (m, 1H), 1.42–1.27 (m, 9H), 1.12 (d, *J* = 6.1 Hz, 3H), 0.87 (t, *J* = 6.4 Hz, 3H); ^{13}C NMR δ 164.3, 143.8, 139.6, 131.5, 129.3, 128.4, 127.6, 124.3, 121.3, 111.6, 111.0, 48.4, 36.9, 32.3, 31.6, 29.1, 25.9, 22.4, 20.5, 14.0. Anal. Calcd for $C_{22}H_{28}N_2OS$: C, 71.70; H, 7.66; N, 7.60. Found: C, 71.92; H, 7.61; N, 7.61.

7-Anilino-4-isopropyl-2-methyl-2*H*-1,4-benzothiazin-3(4*H*)-one (6.3e). Yield 93%, brown microcrystals mp 136–138 °C; ^{1}H NMR δ 7.34 (t, *J* = 7.2 Hz, 2H), 7.25 (t, *J* = 7.3 Hz, 1H), 7.10 (d, *J* = 7.3 Hz, 2H), 6.45 (d, *J* = 2.2 Hz, 1H), 6.20 (d, *J* = 8.7 Hz, 1H), 6.13

(dd, J = 8.9, 2.5 Hz, 1H), 3.55 (q, J = 14.2, 7.0 Hz, 1H), 3.48–3.39 (m, 2H), 1.44 (d, J = 7.2 Hz, 3H), 1.07 (d, J = 6.2 Hz, 6H); ^{13}C NMR δ 167.0, 143.7, 140.1, 131.3, 129.4, 128.5, 127.5, 123.3, 121.0, 111.9, 111.5, 44.2, 38.6, 22.7, 14.8. HRMS calcd for $C_{18}H_{20}N_2OS$ (M): 312.1296, found: 312.1293.

7-Anilino-4-isopropyl-2*H*-1,4-benzothiazin-3(4*H*)-one (6.3f). Yield 89%, white microcrystals mp 87–89 °C; ^{1}H NMR δ 7.35 (t, J = 7.2 Hz, 2H), 7.26 (t, J = 7.3 Hz, 1H), 7.12 (d, J = 7.3 Hz, 2H), 6.46 (d, J = 2.4 Hz, 1H), 6.22 (d, J = 8.8 Hz, 1H), 6.13 (dd, J = 8.8, 2.6 Hz, 1H), 3.47–3.37 (m, 4H), 1.07 (d, J = 6.1 Hz, 6H); ^{13}C NMR δ 164.3, 143.6, 139.5, 131.6, 129.4, 128.4, 127.6, 121.3, 111.8, 111.2, 44.1, 32.3, 22.7. Anal. Calcd for $C_{17}H_{18}N_2OS$: C, 68.42; H, 6.08; N, 9.39. Found: C, 68.42; H, 6.46; N, 9.35.

General Procedure for the Preparation of Benzothiazepinones 6.5a-c. The corresponding 2-alkylthio-1,4-benzenediamine (3.4 mmol) was dissolved in THF (15 mL) in an ice bath and treated with DCC (3.4 mmol). The reaction mixture was allowed to stir at 0 ºC for 1 h and at room temperature for 20 h under nitrogen. THF was evaporated and water (50 mL) was added of to the yellowish slurry and extracted with CH_2Cl_2, dried ($MgSO_4$), and filtered (Celite). The solvent was evaporated and the dark slurry was purified by silica gel column chromatography [Hex: EtOAc (9:1), (7:3) and (1:1)] to give the desired benzothiapinones.

8-Anilino-5-(1,3-dimethylbutyl)-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one (6.5a). Yield 85% (as a 1.3:1 ratio mixture of conformers), yellow microcrystals mp 68–71 °C; ^{1}H NMR δ (major conformer): 7.31 (pseudo t, J = 7.9 Hz, 3H), 7.26–7.05 (m, 3H), 7.00 (t, J = 7.6 Hz, 2H), 6.06 (s, 1H), 4.88–4.81 (m, 1H), 3.29–3.19 (m, 2H), 2.56–2.41 (m,

2H), 1.78–1.66 (m, 1H), 1.56–1.44 (m, 1H), 1.40 (d, *J* = 6.7 Hz, 3H), 1.35–1.13 (m, 1H), 1.11–0.95 (m, 3H), 0.88 (d, *J* = 6.4 Hz, 3H); ^{1}H NMR δ (minor conformer): 7.31 (pseudo t, *J* = 7.9 Hz, 3H), 7.26–7.05 (m, 3H), 7.00 (t, *J* = 7.6 Hz, 2H), 6.06 (s, 1H), 4.79–4.72 (m, 1H), 3.29–3.19 (m, 2H), 2.56–2.41 (m, 2H), 1.78–1.66 (m, 1H), 1.56–1.44 (m, 1H), 1.40 (d, *J* = 6.7 Hz, 3H), 1.35–1.13 (m, 1H), 1.11–0.95 (m, 3H), 0.77 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR δ (major conformer): 172.1, 142.8, 141.8, 136.5, 130.7, 129.4, 126.6, 122.9, 122.0, 118.9, 117.0, 51.4, 45.9, 43.1, 34.6, 25.2, 23.0, 21.1, 18.4; ^{13}C NMR δ (minor conformer): 171.8, 142.8, 141.8, 136.5, 130.6, 129.4, 126.5, 122.9, 122.0, 118.8, 117.0, 51.4, 45.9, 43.1, 33.9, 24.9, 22.4, 21.1, 18.4. Anal. Calcd for $C_{21}H_{26}N_2OS$: N, 7.90. Found: N, 8.01. HRMS calcd for $C_{21}H_{26}N_2OS$ (M): 354.1766, found: 354.1768.

8-Anilino-5-(1-methylheptyl)-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one (6.5b). Yield 97% (as a 1.2:1 ratio mixture of conformers), yellow oil; ^{1}H NMR δ (major conformer): 7.42 (t, *J* = 8.5 Hz, 3H), 7.23–7.19 (m, 1H), 7.12 (d, *J* = 8.8 Hz, 2H), 7.07 (s, 1H), 7.00 (t, *J* = 7.8 Hz, 1H), 6.01 (s, 1H), 4.82–4.60 (m, 1H), 3.29–3.19 (m, 2H), 2.52–2.45 (m, 2H), 1.66–1.53 (m, 1H), 1.41 (d, *J* = 6.7 Hz, 3H), 1.29–1.16 (m, 9H), 0.87 (t, *J* = 6.7 Hz, 3H); ^{1}H NMR δ (minor conformer): 7.42 (t, *J* = 8.5 Hz, 3H), 7.23–7.19 (m, 1H), 7.12 (d, *J* = 8.8 Hz, 2H), 7.07 (s, 1H), 7.00 (t, *J* = 7.8 Hz, 1H), 6.01 (s, 1H), 4.79–4.72 (m, 1H), 3.29–3.19 (m, 2H), 2.52–2.45 (m, 2H), 1.66–1.53 (m, 1H), 1.41 (d, *J* = 6.7 Hz, 3H), 1.29–1.16 (m, 9H), 0.84 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR δ (major conformer) 172.1, 142.8, 141.8, 137.0, 130.7, 129.4, 128.7, 126.7, 122.9, 118.9, 117.0, 53.0, 37.0, 33.9, 31.8, 29.3, 26.9, 22.6, 20.8, 18.2, 14.1; ^{13}C NMR δ (minor conformer) 171.8, 146.6, 142.6, 136.5, 130.4, 127.4, 127.1, 126.6, 126.3, 122.0, 118.8, 54.2, 34.5, 31.7, 29.1, 26.9, 26.1, 22.5, 20.8, 18.2, 14.1. HRMS calcd for $C_{23}H_{30}N_2OS$ (M): 382.2146, found: 382.2079.

8-Anilino-5-isopropyl-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one (6.5c). Yield 81%, yellow microcrystals mp 163–166 °C; ^{1}H NMR δ 7.37–7.30 (m, 2H), 7.23–7.15 (m, 3H), 6.84 (t, *J* = 2.7 Hz, 1H), 6.80 (d, *J* = 8.8 Hz, 1H), 6.46 (dd, *J* = 2.9, 8.8 Hz, 1H), 3.66–3.48 (m, 2H), 3.40 (br s, 2H), 2.71 (br s, 2H), 1.22 (d, *J* = 6.3 Hz, 6H); ^{13}C NMR δ 171.9, 146.3, 142.3, 136.0, 128.9, 128.8, 127.5, 127.1, 126.3, 118.2, 114.2, 44.2, 34.4, 34.1, 22.9. Anal. Calcd for $C_{18}H_{20}N_2OS$: N, 8.97. Found: N, 8.75. HRMS calcd for $C_{18}H_{20}N_2OS$ (M): 312.1299, found: 312.1296.

CHAPTER 7
GENERAL CONCLUSIONS

The results in Chapters 1 and 2 illustrate how versatile and useful is benzotriazole-mediated chemistry, in the quest to find useful reactions for new methodologies. Our contribution with the synthesis of 2-substituted-1,3-dioxolane provides a short entry for the synthesis of masked aldehydes and due to the remarkable facility with which the latent formaldehyde group can be introduced, it could be useful for multi-step synthesis. Even though our proposed synthetic route to produce *N*-acylbenzotriazole derivatives *via* an acyl carbanion equivalent was only good for benzylic halides as electrophiles, it provides a distinct advantage to produce such adducts by compounds different to those of the corresponding acid or acyl chloride.

Little work has been done in the area of 2-thio-5-amino substituted benzoquinones. We have provided a new, efficient and practical method to design these valuable compounds by an addition/oxidation mode. The advantage of not requiring the presence of at least two good leaving groups in the starting quinone is quite remarkable. The addition of simplicity and availability of the starting materials by this method generates a powerful tool for the design of these novel molecules.

Finally, in Chapters 5 and 6, syntheses of a new class of benzoquinone diimines as well as a new aproach toward the syntheses of benzothiazepinones and benzothiazinones were developed. A significant advantage of these methods is the preferred regioselective introduction of the mercaptan nucleophile at the C-3 position due to the

electron acceptor ability of the *N*-phenyl group at the C-1 position. Both syntheses represent a new contribution in the area of these benzoquinoid derivatives.

LIST OF REFERENCES

The reference citation system employed throughout this dissertation is that from the book series "Comprenhensive Heterocyclic Chemistry II" Pergamon Press, 1996 (Eds. Katritzky, A. R.; Rees, C. W. and Scriven, E.).

Whenever a reference is cited, a number and letter coding is assigned and it will appear in brackets. The first two numbers symbolize the year of publication, the letters represent the journal in which the paper cited was published, and the last numerical symbols represent the page number. Additional notes to this reference system is explained as follows:

1) References are arranged consecutively by year (from the most recent to the oldest), alphabetically by the journal code and then by page number.
2) For each reference, the code is followed by a complete literature citation following the Journal of Organic Chemistry style.
3) For journals which are published in more than one part or volume, such part or volume will be given in parenthesis after the journal code letter.
4) Less commonly used journals, books or patents are given the code "MI" for miscellaneous.
5) For the journals which have changed the name over the years, the same code is used throughout.

00JHC199 For a recent review on benzothiazepinones, see: Levai, A. *J. Heterocyclic. Chem.* **2000**, 199.

00JOC1886 Katritzky, A. R.; Odens, H. H.; Voronkov, M. V. *J. Org.Chem.* **2000**, *65*, 1886.

00JRC01 Katritzky, A. R.; Odens, H. H.; Voronkov, M. V.; Rostek, C. J.; Maender, O. W. *Rubber Chem. Technol.* **2000**, submitted.

00JRC02 Katritzky, A. R.; Odens, H. H; Voronkov, M. V.; Rostek, C. J. Maender, O. W *Rubber Chem. Technol.* **2000**, manuscript in preparation.

99JOC2219 Schwarz, M. K.; Tumelty, D.; Gallop, M. A.; *J. Org. Chem.* **1999**, *64*, 2219.

98AA35 Katritzky, A. R.; Belyakov, S. A. *Aldrichimica* **1998**, *31*, 35.

98CR409 Katritzky, A. R.; Lan, X.; Yang, J. Z.; Denisko, O. V. *Chem. Rev.* **1998**, *98*, 409.

98MI587 Anufriev, V. Ph.; Novikov, V. L.; Maximov, O. B.; Elyakov, G. B.; Levitskry, D. O.; Lebedev, A. V.; Sadretdinov, S. M.; Shvilkin, A. V.; Afonskaya, N. I.; Rudla, M. Ya.; Cherpachenko, N. M. *Bioorg. Med. Chem. Lett.,* **1998**, *8*, 587.

98S153 Katritzky, A. R.; Levell, J. R.; Pleynet, D. P. M. *Synthesis* **1998**, 153.

97JA3840 Namiki, S.; Arai, T.; Fujimori, K. *J. Am. Chem. Soc.*, **1997**, *119*, 3840.

97JA9321 Katritzky, A. R.; Toader, D. *J. Am. Chem. Soc.* **1997**, 119, 9321.

97JOC726 Katritzky, A. R.; Yang, B.; Semenzin, D. *J. Org. Chem.* **1997**, *62*, 726.

97T5839 Florio, S.; Capriati, V.; Colli, G. *Tetrahedron*, **1997**, *53*, 5839.

96HAC365 Katritzky, A. R.; Soleiman, M.; Yang, B. *Heteroatom Chem.* **1996**, *7*, 365.

96SL701 Katritzky, A. R.; Yang, B.; Qian, Y. *Synlett* **1996**, 701.

95H131 Katritzky, A. R., Ignatchenko, A. V., Lang, H.; *Heterocycles*, **1995**, *41*, 131.

95JA12025 Katritzky, A. R.; Xie, L.; Toader, D.; Serdyuk, L. *J. Am. Chem. Soc.* **1995**, *117*, 12025.

95MI1 Hall Jr., H. K.; Padias, A. B.; Williams, P. A.; Gosau, J-M.; Boone, H. W.; Park, D-K. *Macromolecules*, **1995**, *28*, 1.

95MI9 Hall Jr., H. K.; Padias, A. B.; Yahagi, I.; Williams, P. A.; Bruck, M. A.; Drujon, X. *Macromolecules*, **1995**, *28*, 9.

95S503 Katritzky, A. R.; Chang, H.-X.; Yang, B. *Synthesis* **1995**, 503.

95SC1495 Kaye, P. T.; Mphahlele, M. J. *Synth. Comm.***1995**, *25*, 1495.

94JA1691 Chatterjee, M.; Rokita, S. E.; *J. Am. Chem. Soc.,* 1994, *116*, 1690.

94JOC7209 Katritzky, A. R.; Zhang, Z.; Lan, H.; Lan, H. *J. Org Chem.* **1994**, *59*, 7209.

94JPC2883 Nickel, U.; Chen, Y. –H.; Schneider, S. *J. Phys. Chem.* **1994**, *98*, 2883.

94S445 Katritzky, A. Lan, X. *Synthesis* **1994**, 445.

94S917 Bittner, S.; Lempert, D. *Synthesis*, **1994**, *9*, 917.

94ZOR288 Zakatov, V. V.; Dubina, V. L.; Torubarov, I. V. *Zhurnal Organicheskoi Khimii*, **1994**, *30*, 288.

93MI1 Rampe, D.; Triggle, D. J. *Prog. Drug. Res.* **1993**, *40*, 191.

93SC3061 Katritzky, A. R.; Yang, Z.; Cundy, D. J. *Synth. Comm.* **1993**, 3061.

92JOC851 Schwarz, A.; Madan, P. B.; Mohacsi, E.; O'brien, J. P.; Todaro, L. J.; Coffen, D. L. *J. Org. Chem.* **1992**, *57*, 851.

92JHC1605 Lancelot, J. C.; Letois, B.; Rault, S.; Saturnino, C.; Robba, M. *J. Heterocyclic Chem.* **1992**, *29*, 1605.

92JHC11155 Trapani, G.; Latrofa, A.; Reho, A.; Franco, M.; Liso, G.; *J. Heterocyclic Chem.* **1992**, *29*, 1155.

92LAC403 Erker, T.; Bartsch, H. *Liebigs Ann. Chem.* **1992**, *4*, 403.

92LAC843 Katritzky, A. R.; Li, J.; Malhotra, N. *Liebigs Ann. Chem.* **1992**, 843.

92T7817 Katritzky, A. R., Shobana, N.; Pernak, J.; Afridi, A. S.; Fan, W.-Q. *Tetrahedron*, **1992**, *37*, 7817.

91JOC2143 Katritzky, A. R.; Yang, Z.; Lam, J. N. *J. Org. Chem.* **1991**, *56*, 2143.

91JOC5808 Grennberg, H.; Gogoll, A.; Backvall, J.-E.; *J. Org. Chem.* **1991**, *56*, 5808.

91MI02 Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, John Wiley & Sons, Inc.: New York, **1991**.

91MI1781 Huning, S.; Günther, E.; Meixner, H.; Metzenthin, T.; von Schütz, J. U.; Bair, M.; Groß, H. –J.; Langohr, U.; Söderholm, S.; Werner, H. –P.; Wolf, H. C.; Tillmanns, E. *Synthetic Metals*, **1991**, *41-43*, 1781.

91T2683 Katritzky, A. R.; Rachwal, S.; Hitchings, G. J. *Tetrahedron*, **1991**, *47*, 2683.

90BCJ1258 Shibagaki, M.; Takahashi, K.; Kuno, H.; Matsushita, H. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1258.

90CPB407 Narita, H.; Gaino, M.; Suzuki, T.; Kurosawa, H.; Inoue, H.; Nagao, T.; A. *Chem. Pharm. Bull.*, **1990**, *38*, 407.

90JCSP(1)393 Davies, S. G.; Goodfellow, C. *L. J. Chem. Soc., Perkin Trans. 1* **1990**, 393.

90JCSP(1)1717 Katritzky, A. R.; Rachwal, S.; Rachwal, B. J. *Chem. Soc.Perkin Trans. 1* **1990**, 1717.

90JOC5572 Floyd, D. M.; Moquin, R. V.; Atwal, K. S.; Ahmed, S. Z.; Spergel, S. H.; Gougoutas, J. Z.; Malley, M. F. ; *J. Org. Chem.* **1990**, *55*, 5572.

90SC2387 Houghton, R. P.; Dunlop, J. E. *Synth. Commun.* **1990**, 20, 2387.

89JCSP(1)179 Brimble, M. A.; Brimble, M. T.; Gibson, J. J.; *J. Chem. Soc., Perkin Trans. (1)*, 1989, 179.

89JCS(P1)225 Katritzky, A. R.; Yannakopoulou, K.; Lue, P.; Rasala, D.; Urogdi, L. *J. Chem. Soc. Perkin Trans. 1* **1989**, 225.

89MI01 Corey, E. J.; Cheng, X.-M. *The Logic of Chemical Synthesis*, John Wiley & Sons, Inc.: New York, **1989**.

89MI02 WO 09108189 A1, **1989**. Novikov, V. L.; Anufriev, V. F.;Levitsky, D. O.; Lebedev, A. V.; Sadretdinov, S. M.; Shvilkin, A. V.; Afonskaya, N. I.; Ruda, M. Ya.; Cherepachenko, N. M.; *Chem. Abstr.*, **1989**, *115*, 182874m.

88CGC608 Borovkov, V. V.; Filippovich, E. I.; Evstigneeva, R. P.; *Khim. Geterocycl. Soed.*, **1988**, 608.

88JCSP(1)3399 Johnson, G. P.; Marples, B. A. *J. Chem. Soc., Perkin Trans. 1* **1988**, 3399.

88MI01 Eur. Pat. 262984, 1988. Hiromitsu, S.; Yoichi, U.; Akira, S.; Tadashi, H.; Makoto, M.; Tadashi, A. *Chem. Abstr.*, **1988**, *109*, 92665r.

88MI135 Inada, Y.; Itoh, K.; Kamiya, K.; Sugihara, H.; Nishikawa, K.; *Japan. J. Pharmacol.*, **1988**, *47*, 135.

88MI1231 Brown, E. R. in *The Chemistry of the Quinonoid Compounds* (ed. Patai, S., Rappoport, Z.) John Wiley and Sons Ltd, London, page 1231, **1988**.

87MI29 Berger; S.; Hertl; P.; Rieker, A. in *The Chemistry of The Quinonoid Compounds* (Ed. S. Patai), John Wiley and Sons, London, pages 26-29, **1987**.

87S724 Ambrogi, V.; Grandolini, G.; *Synthesis* **1987**, 724.

87TL5877 Matsukawa, M.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1987**, *28*, 5877.

87ZOR1215 N. P. Bezverkhii, S. I. Protashchuk, N. D. Borodavko, *Zhurnal Organicheskoi Khimii* **1987**, *28*, 1215.

86JOC189 Klaveness, J.; Rise, F.; Undheim, K. *J. Organomet. Chem.* **1986**, *303*, 189.

86JOC536 Giordano, C. *J. Org. Chem.* **1986**, *51*, 536.

86MI02 JP 62273947, **1986**. Itaru, O.; Makoto, N.; Hisao, W.; Hiroyuki, S.; Koji, K. *Chem. Abstr.*, **1986,** 10968848g.

86MI159 Taimr, L.; Pivcová, H.; Pospíšil, J. *Polymer Degradation and Stability*, **1986**, *16*, 159.

86T2731 Balasubramaniyan, V.; Balasubramaniyan, P.; Shaikh, A. S. *Tetrahedron*, **1986**, *42*, 2731.

86T3731 Dilworth, B. M.; Mckervey, M. A. *Tetrahedron* **1986**, *42*, 3731.

86ZOR461 Bezverkhii, N. P.; Protashchuk, S. I. *Zhurnal Organicheskoi Khimii* **1986**, *22*, 461.

85JMC1517 Slade, J.; Stanton, J. L.; Ben-David, D.; Mazzenga, G. C. *J. Med. Chem.* **1985**, *28*, 1517.

85LAC869 Duddeck, H.; Kaiser, M.; Lévai, A. *Liebigs Ann. Chem.* **1985**, 869.

85MI2 Chaffman, M.; Brogden, R. N. *Drugs* **1985**, *29*, 387.

85TL4767 Kamitori, Y.; Hojo, M.; Masuda, R.; Yoshida, T. *Tetrahedron Lett.* **1985**, *26*, 4767.

84AGE447 Aumuller, A.; Hunig, S. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 447.

84BCJ1405 Merchant, J. R.; Martyres, G.; Shinde, N. M. *Bull. Chem. Soc. Jpn.*, **1984**, *57*, 1406.

84KGS1252 Granik, V. G.; Ershov, L. V.; Grizik, S. I.; Chistyakov, V. V. *Khim. Geterocycl. Soedin.* **1984**, *9*, 1252.

84PJC805 Abramovitch, R. A.; Bachoswka, B.; Tomasik, P. *Pol. J. Chem.*, **1984**, 58, 805.

84ZOR1040 Bezverkhii, N. P.; Zinukhov, V. D.; Kremlev, M. M.; Kachanov, A. V.; Litvincheva, T. N. *Zhurnal Organicheskoi Khimii*, **1984**, *20*, 1040.

83JOC4764 Takata, T.; Tajima, R.; Ando, W. *J. Org. Chem.*, **1983**, *48*, 4764.

82JCR(S)138 Greenhalgh, C. W.; Shand, C. A.; Thomson, R. H. *J. Chem. Research (S)*, **1982**, 138.

82MI695 Nickel, U.; Jaenicke, W. *Ber. Bunsenges Phys. Chem.*, **1982**, *86*, 695.

82S956 Olah, G. A.; Narang, S. C.; Mehrotra, A. K. *Synthesis* **1982**, 956.

81IJC995 R. G. Srivastava, R. L. Pandey, P. Venkataramani, *Indian, J. Chem.*, **1981**, *20B*, 995.

81JCSP(1)2970 Gupta, D. N.; Hodge, P.; Davies, J. E. *J. Chem. Soc., Perkin Trans. (1)*, **1981**, 2970.

80BCJ3619 Tanaka, K.; Matsui, S.; Kaji, A. *Bull. Chem. Soc. Jpn.* 1980, *53*, 3619.

80JCSP(1)756 Houghton, R. P.; Morgan, A. D. *J. Chem. Soc., Perkin Trans. 1* **198**0, 756.

80JHC793 Liso, G.; Trapani, G.; Berardi, V.; Latrofa, A.; Marchini, P.; *J. Heterocyclic Chem.* **1980**, 793.

80JOM141 Gasparani, J. P.; Gassend, R.; Maire, J. C.; Elguero, J. *J. Organometallic Chem.* **1980**, *188*, 141.

80TL1559 Kocienski, P. J. *Tetrahedron Lett.* **1980**, *21*, 1559.

79MI7 Barton, D.; Ollis, W. D. *Comprenhensive Organic Chemistry*; Pergamon Press: Oxford, **1979**.

79MI877 Nickel, U.; Borchardt, M.; Bapat, M. R.; Jaenicke, W. *Ber. Bunsenges Phys. Chem.*, **1979**, *83*, 877.

78TL2345 Ncube, S.; Pelter, A.; Smith, K.; Blatcher, P.; Warren, S. *Tetrahedron Lett.* **1978**, *26*, 2345.

77AGE266 Nickel, U.; Kemnitz, K. *Angew. Chem. Int. Ed. Engl.* **1977**, 16, 266.

77JOM185 Gassend, R.; Maire, J. C.; Pommier, C. *J. Organometallic Chem.* **1977**, *137*, 185.

77MI171 Vorkapic-Furac, J.; Kishi, T.; Kishi, H.; Porter, T. H., Folkers, K. *Acta Pharm. Suec.* **1977**, *14*, 171.

77MI276 Tanimoto, S., Miyake, T., Okano, M. *Bull. Inst. Chem. Res., Kyoto Univ.*, **1977**, *Vol. 55*, No. 3, 276.

77MI339 Tong, L. K. J.; In *The Theory Of The Photograhic Process*, 4th Ed. (Ed. James T. H.) Macmillian, New York, Page 339, **1977**.

77S357 Gröbel, B.-T.; Seebach, D. *Synthesis*, 1977, 357.

77TL885 Kruse, C. G.; Broekholf, N. L. J. M.; Wijsman, A.; Van Der Gen, A. *Tetrahedron Lett.* **1977**, *10*, 885.

77TL2077 Taylor, E. C.; Lamattina, J. L. *Tetrahedron Lett.* **1977**, *24*, 2077.

76JCSP(1)2343 Bose, A. K.; Hoffman III, W. A.; Manhas, M. S.; *J. Chem. Soc., Perkin Trans. 1* **1976**, 2343.

76MI6 Krapcho, J. (E.R. Squibb And Sons Inc.) U.S. Patent 348,433 (**1976**); *Chem. Abstr.*, **1976**, *84*, 180247b.

76T1943 Lever, O.W. *Tetrahedron*, **1976**, *32*, 1943.

76TL4223 Sachdev, K.; Sachdev, H. S. *Tetrahedron Lett.* **1976**, 4223.

76ZOR2479 Kremlev, M. M.; Bezverkhii, N. P.; Burmistrov, S. I. *Zhurnal Organicheskoi Khimii* **1976**, *12*, 2479.

74CIL687 Seebach, D.; Kolb, M. *Chem. Ind.,* **1974**, 687.

74JCS(P1)2208 Forrester, A. R.; Hepburn, S. P. *J. Chem. Soc., Perkin Trans. 1*, **1974**, 2208.

74MI001 Berger, S.; Hertl, P.; Rieker, A.; in *The Chemistry of The Quinonoid Compounds*, Vol.II, (Ed. Patai, S.), John Wiley and Sons, **1974**.

73CPB92 Nagao, T.; Sato, M.; Nakajima, H.; Kiyomoto, A. *Chem. Pharm. Bull.*, **1973**, *21*, 92.

73MI103 Corbett, J. F. *J. Soc. Cosmet. Chem.* **1973**, *24*, 103.

73MI4 Yamada, K.; Shimamura, T.; Nakajima, H.; *Japan. J. Pharmacol.*, **1973**, *23*, 321.

73T147 Hunter, P. W. W.; Webb, G. A. *Tetrahedron* **1973**, *29*, 147.

73TL4696 Cajipe, G.; Rutolo, D.; Moor, H. W. *Tetrahedron Lett.*, **1973**, *47*, 4695.

72MI3 Nagao, T.; Nakajima, H.; Kiyomoto, A. *Japan. J. Pharmacol.*, **1972**, *22*, 1.

71JA1347 Baetzold, R. C.; Tong, L. K. J. *J. Am. Chem. Soc.* **1971**, *93*, 1347.

71S312 Kabusz, S.; Tritschler, W. *Synthesis* **1971**, 312.

71TL3151 Ogura, K.; Tsuchihashi, G. *Tetrahedron Lett.* **1971**, 3151.

70MI663 Finley, K. T.; Tong, L. K. J. in *The Chemistry of the Carbon-Nitrogen Double Bond,* (Ed. Patai, S.), Interscience (John Wiley and Sons), London, page 663, **1970**.

70TL1457 Kreutzberger, A.; Dietz, E. *Tetrahedron Lett.* **1970**, *17*, 1457.

69T3641 Honzl, J.; Metalová, M. *Tetrahedron* **1969**, *25*, 3641.

69T4153 Holland, V. R.; Saunders, B. C. *Tetrahedron* **1969**, *25*, 4153.

66JOC4097 Corey, E. J.; Seebach, D. J. *J. Org. Chem.* **1966**, *31*, 4097.

65AGE1075 Corey, E. J.; Seebach, D. *Angew. Chem., Int. Ed. Engl.*, 1965, *4*, 1075.

61LAC641 Meerwein, H.; Florian, W.; Schon, N.; Stopp, G. *Liebigs Ann. Chem.* **1961**, *1*, 641.

59CB245 Neunhoeffer, O.; Heitmann, P. *Chem. Ber.*, **1959**, 245.

59JACS1721 Kirchner, F. K.; Alexander, J.; *J. Am. Chem. Soc* **1959**, *81*, 1721.

58ACS1 Lawesson, S.-O. *Acta Chem. Scan*d. **1958**, *12*,1.

58CB650 Bagana, H.; Domaschke, L. *Ber. Dtsch. Chem. Ges.* **1958**, *91*, 650.

57AG252 Gauss, W.; Petersen, S. *Angew. Chem.*, **1957**, *69*, 252.

57HCA502 Marxer, A. *Helv. Chim. Acta*, **1957**, 502.

56JA1233 Crosby, A. H.; Lutz, R. E. *J. Am. Chem. Soc.*, **1956**, *78*, 1233.

56JCS3814 Hughes, G. M. K.; Saunders, B. C. *J. Chem. Soc.*, **1956** 3814.

56MI724 Jolles, Z. E. (Ed. E. H. Rodd), in *Chemistry of Carbon Compounds*, Elsevier, Amsterdam, Vol. 3, page 724, **1956**.

55AG217 Petersen, S.; Gauss, W.; Urbschat, E. *Angew. Chem.*, **1955**, *67*, 217.

54JA285 Gaylord, N. G. *J. Am. Chem. Soc.* **1954**, *76*, 285.

52JCS4040 Sondheimer, F. *J. Chem. Soc.* **1952**, 4040.

52RTC1021 Wibaut, J. P.; Huls, R. *Rec. Trav. Chim.* **1952**, *71*, 1021.

51JA1149 Adams, R.; Eilar, K. R. *J. Am. Chem. Soc.* **1951**, *73*, 1149.

50JA4601 Adams, R.; Nagarkatti, A. S. *J. Am. Chem. Soc.* **1950**, *72*, 4601.

49JA1124 Little, J. E.; Sproston, T. J.; Foote, M. W. *J. Am. Chem. Soc.*, **1949**, *71*, 1124.

48JA861 Baltzly, R.; Lorz, E. *J. Am. Chem. Soc.*, **1948**, *70*, 861.

47JCS2233 Deno, N. C. *J. Chem. Soc.* **1947**, 2233.

10CB525 Fischer, E.; Schrader, H. *Chem. Ber.*, **1910**, 525.

04CB4605 Willstätter, R.; Pfannenstiehl, A. *Chem. Ber.*, **1904** *37*, 4605.

1897CB608 Unger; O. *Chem. Ber.* **1897**, *30*, 608.

1897CB2393 Unger; O.; Graff, G. *Chem. Ber.* **1897**, *30*, 2393.

BIOGRAPHICAL SKETCH

Herman Howard Odens was born on March 10, 1968, in David, Panama. He graduated in 1992 from The University of South Alabama in Mobile, Alabama, with a Bachelor of Science degree with a major in chemistry and a minor in mathematics. From October 1992 to December 1994, he worked as an industrial chemist at Commercial & Industrial Dixie, S.A., in Panama City, Panama – a Division in Central America of the Bullen Chemical Co., Chicago, IL.

In January of 1995 he came back to the United States to pursue his Master of Science degree in organic chemistry which he received in May 1997 from West Virginia University under the supervision of Dr. Björn C. Söderberg.

In August 1997, he began the graduate program at the Department of Chemistry of the University of Florida under the supervision of Professor Alan R. Katritzky. On December 8, 2000, he successfully defended his doctorate dissertation at the University of Florida and obtained his Doctor of Philosophy degree in May 2001.

He is married to Noemi Odens and has three sons, Herman Jr., and twin-babies, Jake and Jeremy. His favorite hobbies include outdoor sports, karate and watching Japanese cartoons with his sons.

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a thesis for the degree of Doctor of Philosophy.

Alan R. Katritzky, Chair
Kenan Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a thesis for the degree of Doctor of Philosophy.

Lisa McElwee-White
Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a thesis for the degree of Doctor of Philosophy.

Eric Enholm
Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a thesis for the degree of Doctor of Philosophy.

Alexander Angerhofer
Associate Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a thesis for the degree of Doctor of Philosophy.

Ulrich H. Kurzweg

Ulrich Kurzweg
Professor of Aerospace Engineering,
Mechanics and Engineering Science

This thesis was submitted to the Graduate Faculty of the Department of Chemistry in the College of Liberal Arts and Sciences and to the Graduate School and was accepted as partial fulfillment of the requirements for the degree of Doctor of Philosophy.

May, 2001

Dean, Graduate School